TABLE 33
Classification of *H. pylori* Infection, Evaluability, and Eradication Based on Endoscopic Tests for *H. pylori* at Baseline All Randomized Patients (Study #127)

Pre-therapy (Baseline) Diagnosis					
Culture	Histology	CLOtest® †	Patient Status	O 20 bid + A 1000 bid + C 500 bid (N = 86)	A 1000 bid + C 500 bid (N = 85)
Three tests available					
+	+	+	Infected	60	68
+	+	–	Infected	—	—
+	–	+	Infected	0	0
+	–	–	Infected	—	—
–	+	+	Infected	11	11
–	–	+	Not infected	5	1
–	+	–	Not infected	—	—
–	–	–	Not infected	1*	0
Two tests available					
+	+	N/A	Infected	—	—
+	–	N/A	Infected	—	—
–	+	N/A	Not evaluable	—	—
–	–	N/A	Not infected	1*	0
+	N/A	+	Infected	1	0
+	N/A	–	Infected	—	—
–	NA	+	Not evaluable	0	0
–	NA	–	Not infected	—	—
N/A	+	+	Infected	6	4
N/A	+	–	Not evaluable	—	—
N/A	–	+	Not evaluable	0	1
N/A	–	–	Not infected	1*	0
One test available					
+	N/A	N/A	Infected	—	—
–	N/A	N/A	Not evaluable	—	—
N/A	N/A	+	Not evaluable	0	0
N/A	N/A	–	Not evaluable	—	—
N/A	+	N/A	Not evaluable	—	—
N/A	–	N/A	Not evaluable	—	—

† Patient must have positive CLOtest® to receive study medication and to be included in the study.

* Three patients were entered into the study and took study medication even though the baseline CLOtest® was negative or unavailable.

TABLE 34
Classification of *H. pylori* Infection, Evaluability, and Eradication Based on Endoscopic Tests for *H. pylori* at Week 8 All Randomized Patients (Study #127)

Post-therapy (Week 8) Diagnosis					
Culture	Histology	CLOtest®	Patient Status	O 20 bid + A 1000 bid +C 500 bid (N = 86)	A 1000 bid + C 500 bid (N = 85)
Three tests available					
+	+	+	Infected	6	29
+	+	–	Infected	0	6
+	–	+	Infected	0	1
+	–	–	Infected	1	0
–	+	+	Infected	1	4
–	–	+	Infected	3	1
–	+	–	Infected	1	0
–	–	–	Eradicated	58	30
Two tests available					
+	+	N/A	Infected	0	0
+	–	N/A	Infected	0	0
–	+	N/A	Infected	0	0
–	–	N/A	Eradicated	0	0
+	N/A	+	Infected	0	0
+	N/A	–	Infected	0	0
–	NA	+	Infected	0	0
–	NA	–	Eradicated	0	0
N/A	+	+	Infected	0	2
N/A	+	–	Infected	0	1
N/A	–	+	Infected	0	0
N/A	–	–	Eradicated	3	2
One test available					
+	N/A	N/A	Infected	0	0
–	N/A	N/A	Not evaluable	0	0
N/A	N/A	+	Infected	0	0
N/A	N/A	–	Not evaluable	1	0
N/A	+	N/A	Infected	0	0
N/A	–	N/A	Not evaluable	0	0
Zero tests available					
N/A	N/A	N/A	Not evaluable	12	9

Ulcer healing rates at week 8 are presented in Table 35 for the per-protocol analysis.

TABLE 35
Duodenal Ulcer Healed Status by Week 8
Per-Protocol and Intent-to-Treat Analyses

Study #127

	O 20 bid + A 1000 bid + C 500 bid	A 1000 bid + C 500 bid
	n/N (%)	n/N (%)
Per-Protocol Analysis	54/66 (82%)	53/67 (79%)
By baseline smoking status		
Smokers	18/27 (67%)	25/32 (78%)
Non-smokers	36/39 (92%)	28/35 (80%)
Intent to Treat Analysis	59/77 (77%)	57/83 (69%)

Note: There was a significant interaction between baseline smoking status and treatment group ($p \leq 0.100$), using a logistic regression model for the per-protocol analysis

Note: There were no significant differences between the treatment groups, overall ($p = 0.75$) or separated by baseline smoking status ($p = 0.33$ for smokers and $p = 0.13$ for non-smokers), using logistic regression models for the per-protocol analysis

Note: There was no significant difference between the treatment groups in the intent-to-treat analysis, with respect to the overall duodenal ulcer healing rates ($p=0.320$), using a logistic regression model.

The relationship between *H. pylori* eradication and duodenal ulcer healing by Week 8 is displayed in Table 36. For both treatment groups combined, 84% of the patients (66 of 79 patients) who were considered *H. pylori* eradicated at Week 8 also had a healed duodenal ulcer by Week 8. Of the patients who were considered to not have *H. pylori* eradication at Week 8, 75% of the patients (36 of 48 patients) had a healed duodenal ulcer by Week 8.

TABLE 36
Duodenal Ulcer Healed Status by Week 8 vs. *H. pylori* Eradication Status at Week 8
Number of Patients
Per-Protocol Analysis

Study #127

	O 20 bid + A 1000 bid + C 500 bid			A 1000 bid + C 500 bid			Both treatment groups combined		
	Duodenal Ulcer Healed by Week 8								
H. pylori Eradicated at Week 8	Yes	No	Total	Yes	No	Total	Yes	No	Total
Yes	41	10	51	25	3	28	66	13	79
No	9	1	10	27	11	38	36	12	48
Total	50	11	61	52	14	66	102	25	127
Fisher's Exact Test p-value:	p = 0.673			p = 0.126			p = 0.258		

Note: There were no significant associations observed between *H. pylori* eradication at Week 8 and duodenal ulcer healed status by Week 8 ($p > 0.050$), using Fisher's Exact Test.

Table 37 and Figure 3 show the time until patients were free of ulcer symptoms. There was no significant difference in the time-to-event curves for the time until patient is free of ulcer symptoms between the O 20 bid + A 1000 bid + C 500 bid group and the A 1000 bid + C 500 bid group and the median time until patients were free of ulcer symptoms was similar in both groups.

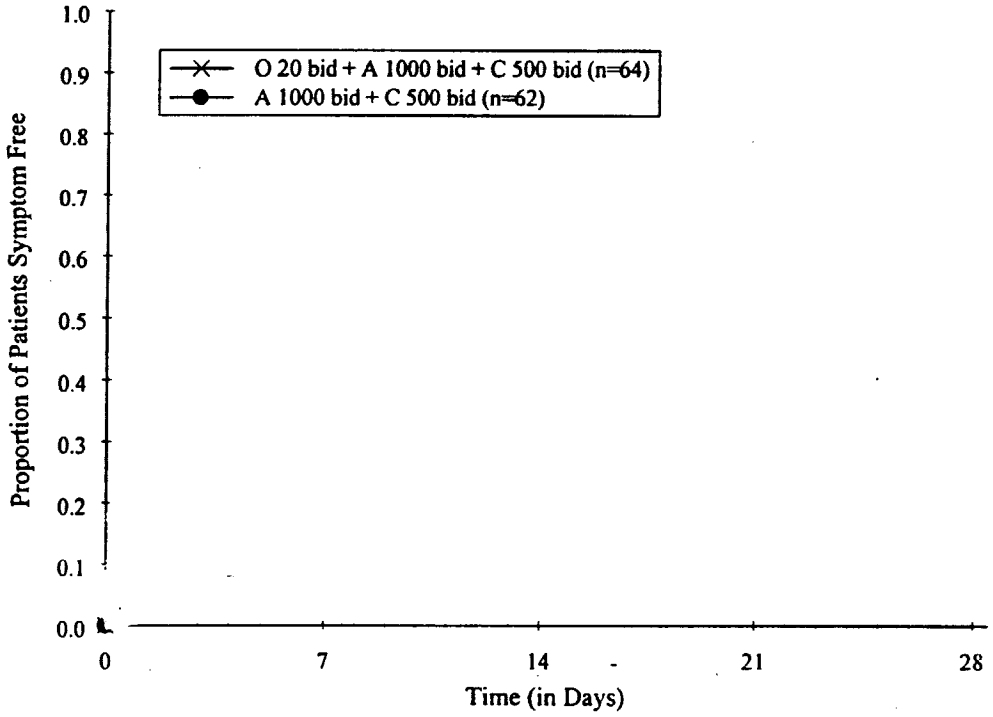
TABLE 37
Time Until Patient Is Free of Ulcer Symptoms (in Days)
Per-Protocol Analysis

Study #127

Percentiles	O 20 bid +A 1000 bid + C 500 bid (N = 64)	A 1000 bid +C 500 bid (N = 62)
25th %	5 days	7 days
50th % (Median)	24 days	25 days
75th %	> 28 days	> 28 days

Note: There was no significant difference between the time-to-event curves for O 20 bid + A 1000 bid + C 500 bid vs. A 1000 bid + C 500 bid, (p=0.959), using Cox's proportional hazards regression model.

FIGURE 3
TIME UNTIL PATIENT IS FREE OF ULCER SYMPTOMS
PER-PROTOCOL ANALYSIS
Study #127



Similar to study 126, mean daily GELUSIL usage was less than 1 tablet per day, but increased in the antibiotic alone arm. GELUSIL usage is outlined in Table 38.

TABLE 38
Average GELUSIL® Usage (in tablets per day) - Days 1 through 28
Per-Protocol Analysis

Study #127

Treatment Group	N	Mean	SD	Range
O 20 bid + A 1000 bid + C 500 bid	65	0.54	0.88	0 to 4.21
A 1000 bid + C 500 bid	67	0.72	1.07	0 to 4.86

Note: No statistical comparisons were made between treatment groups.

SAFETY

The number of clinical adverse event and laboratory adverse events are summarized in Table 39 and 40, respectively.

TABLE 39
Clinical Adverse Events Summary
Number (%) of Patients, Weeks 1 through 8
All Randomized Patients Who Took At Least One Dose of Study Medication
Study #127

	O 20 bid + A 1000 bid + C 500 bid (N = 85)	A 1000 bid + C 500 bid (N = 85)
Number (%) of Patients:	n (%)	n (%)
With ≥ 1 clinical adverse event	48 (56%)	49 (58%)
With a possibly or probably drug-related clinical adverse event	29 (34%)	25 (29%)
With a serious clinical adverse event	1 (1%)	0 (0%)
Discontinued due to a clinical adverse event	4 (5%)	4 (5%)

Note: There were no significant differences observed between the treatment groups ($p>0.050$), using a Fisher's Exact Test.

TABLE 40
Laboratory Adverse Events Summary
Number (%) of Patients
Weeks 1 through 8
All Randomized Patients Who Took At Least One Dose of Study Medication†

Study #127

	O 20 bid + A 1000 bid + C 500 bid (N = 84) †	A 1000 bid + C 500 bid (N = 83) †
Number (%) of Patients:	n (%)	n (%)
With ≥ 1 laboratory adverse event	8 (10%)	10 (12%)
With possibly or probably drug-related laboratory adverse event	1 (1%)	0 (0%)
Serious laboratory adverse event	0 (0%)	0 (0%)
Discontinued due to laboratory adverse event	0 (0%)	0 (0%)

† Number of patients who took at least one dose of study medication and who had any laboratory tests performed after baseline.

Note: There were no significant differences observed between the treatment groups, ($p>0.050$), using a Fisher's Exact Test.

REVIEWERS' CONCLUSIONS FOR STUDY 127

This was a well conducted, randomized, clinical trial which convincingly demonstrated the superiority of triple therapy (O + A + C) over antibiotics alone (A + C) when given for 10 days with twice daily dosing. The lower bound of the 95% confidence interval of the point estimate for triple therapy using the ITT analysis was 63%, more than the 60 percent threshold as suggested by the Division.

In addition, multiple interesting observations were made:

- *In contrast to study 126, the per-protocol eradication rate was statistically higher among smokers as compared with non-smokers for the triple therapy arm but lower among smokers as compared with non-smokers for the dual therapy arm. Note, however, that several smokers in the triple therapy arm did not have H. pylori eradication information at follow-up (5 patients in the per-protocol analysis).*

- *The false negative rate of CLOtest at the follow-up visit as compared with culture (alone) and histology (alone) was quite high (16% and 16%, respectively). These results were similar to those found for study 126 and casts doubt on the utility of the CLOtest to monitor the effectiveness of treatment.*
- *Like study 126, there was no significant difference in ulcer incidence rates at 4 weeks post-treatment between the triple therapy and antibiotic alone arms (82% versus 79%, per-protocol; 77% versus 69%, intent-to-treat). This suggests that antibiotics alone may be sufficient to achieve adequate ulcer healing at 4 weeks post-treatment.*
- *H. pylori eradication was associated with a numerically better ulcer healing rate at the 4-week follow-up visit (84%) as compared with the healing rate among patients who were not eradicated of H. pylori (75%) when combining treatment groups.*
- *The median time to resolution in ulcer symptoms was similar in the triple therapy and antibiotic only arms and there was no difference between treatment groups in the time to resolution curves. Similar to study 126, the mean gelusil usage for antibiotic only therapy was more than that of triple therapy.*
- *The proportion of patients with adverse events (and related adverse events) was similar between treatment groups*

MEDICAL AND STATISTICAL REVIEW OF ABBOTT STUDY 56268

INVESTIGATORS

The study utilized three central laboratories. , in was used for laboratory tests. Dr. David Graham and Dr. Michael Osato's laboratory was used for microbiology specimens. Histology specimens were sent to Robert Genta and Hala el Zimaity at the VA Medical Center, Houston, Texas. The clinical investigators are shown in Table 41.

Table 41: Distribution of All Randomized Patients by Investigator: Study 56268

	Treatment Group			Treatment Group	
Investigator	C+A+O	C+A	Investigator	C+A+O	C+A
Aaronson	2	2	Movva	4	4
Attar	0	2	Pambianco	1	2
Barish	0	2	Peura	0	1
Barreiro	3	2	Pruitt	2	2
Bell	0	1	Ramirez	2	2
Berry	1	0	Reymunde	14	12
Brady	2	2	Rosenberg	2	3
Brayko	2	3	Roubein	2	2
Caos	2	2	Rubin	6	5
Cave	1	0	Sabesin	1	0
Chen	1	0	Safdi	0	1
Cline	5	5	Schwartz	2	4
Cutler	2	3	Shah	12	12
DeMicco	3	3	Shivakumar	2	2
Fitch	1	1	Silverman	1	0
Fusilier	0	1	Simmons	5	5
James	1	2	Sontag	1	1
Kogut	1	1	Spiotta	3	2
Kruss	0	1	Sutton	0	1
Lanza	5	4@	Vakil	1	2
Levenson	2	1	Winston	1	1
Loludice	5	4	Wruble	3	3
Martin	2	2	**Total**	**106**	**111**

@ One patient did not take study medication

STUDY OBJECTIVE

The sponsor stated the objective of this study to be: "to compare the safety and efficacy of combination therapy with clarithromycin, amoxicillin, and omeprazole (C+A+O) to combination therapy with clarithromycin and amoxicillin (C+A) for the eradication of *H. pylori* from the gastric mucosa in patients with a history of duodenal ulcer disease who did not have an active ulcer."

STUDY DESIGN

This was a Phase III, double-blind, randomized, parallel group, multicenter study in adult patients who had a history of duodenal ulcer disease but did not have an active ulcer. Endoscopy was to be performed on each patient within 14 days pretreatment in order to confirm the absence of a duodenal ulcer. Patients who had a duodenal ulcer were to be allowed to be treated with an H_2-blocker for a minimum of six weeks and reassessed by endoscopy prior to study enrollment. If the ulcer was healed at the time of the repeat endoscopy and erosions were not present, the patient could have been enrolled in the study. At the time of endoscopy, biopsies were to be taken from the antrum and corpus to confirm the presence of *H. pylori* by CLOtest, culture, and histology. The clinical signs and symptoms of ulcer disease were documented. A patient who fulfilled all selection criteria was randomized to begin study medication. Patients were randomly assigned in a 1:1 ratio to receive ten days of either:

clarithromycin 500 mg BID + amoxicillin 1000 mg BID + omeprazole 20 mg BID	OR	clarithromycin 500 mg BID + amoxicillin 1000 mg BID + placebo BID

After the completion of the 10-day treatment, patients were to be instructed to return to the investigator's office for safety evaluation and assessment of signs and symptoms at the Post-treatment Visit which occurred one to four days after the patient completed study medication. The final visit (4 to 6 Week Follow-up) was to occur within 28 to 42 days after the patient completed study medication. At this visit an endoscopy with biopsies was to be performed for evaluation of efficacy and an assessment of signs and symptoms was performed. If at any time during the study the signs/symptoms of ulcer disease were present and did not resolve or improve after five days of taking antacids, the patient was to be instructed to contact the investigator. At the investigator's discretion an unscheduled visit could be conducted. The procedures required at the 4 to 6 Week Follow-up Visit were to be performed at an Unscheduled Visit; the endoscopy with biopsies was not required, however, it could have been performed if clinically indicated.

The schedule of visits is outlined in Table 42.

Table 42: Schedule of Visits

Visit	Pretreatment	Post-treatment	4-6 Week Follow-up	
Study Procedures	**Within 14 Days Prior to Therapy**	**Day 11-14**	**28 to 42 Days After the Last Dose**	**Unscheduled Visit**
Informed Consent	X			
Medical History	X			
Serology for *H. pylori*	X			
Social History	X			
Physical Examination	X	X	X	X
Vital Signs	X	X	X	X
Signs and Symptoms	X	X	X	X
Endoscopy	X		X	X@
Biopsy: Culture & Histology	X		X	X@
Biopsy: CLOtest	X		X	X@
Laboratory Tests	X	X		
Dispense Medication	X			
Evaluate Study Drug Compliance		X		
Monitoring of Adverse Events		X	X	X
Evaluate Concomitant Medication Use		X	X	X
@ If clinically indicated.				

INCLUSION/EXCLUSION CRITERIA

The inclusion and exclusion criteria were similar to the Astra-Merck Studies 126 and 127 with the following difference:

- Patients were to have no active duodenal ulcer (as confirmed by endoscopy); however, the patient must have had a history of duodenal ulcer (as confirmed by endoscopy or upper GI radiogram) within 5 years prior to study start.

Medical Officer Comment: Of note is that the case report form has the following statement with regard to a history of duodenal ulcer in the inclusion criteria section:

"The patient has a history of duodenal ulcer, demonstrated by endoscopy or upper GI radiogram within the past 5 years.

Endoscopy source:

Medical Record (i.e. copy of EGD exam, chart notes)
Referral from Physician (copy of referral letter)
Description from patient

GI Radiogram source

Medical Record (i.e. copy of EGD exam, chart notes)

Referral from Physician (copy of referral letter)
Description from patient

Hence, it is possible that a certain number of patients were diagnosed with duodenal ulcer disease based on their recollection of a test result in the past.

On April 16, the medical officer requested the sponsor to break down the number of patients in each of these categories as shown below:

	Number
Endoscopy source:	***195***
Medical Record (i.e. copy of EGD exam, chart notes	*146*
Referral from Physician (copy of referral letter)	*1*
Description from patient	*51*
GI Radiogram source:	***28***
Medical Record (i.e. copy of EGD exam, chart notes	*10*
Referral from Physician (copy of referral letter)	*0*
Description from patient	*19*

It can be seen that the majority of patients who were included in the study had a past history of ulcer documented by endoscopy and most of these were documented by medical records rather than a description from the patient.

PATIENT REMOVAL

Patients were to be withdrawn from study drug therapy immediately if any of the following occurred:

- The patient received any anti-ulcer medication in dosages indicated for ulcer disease which would interfere with the evaluation of therapy.
- The investigator decided it was in the best interest for the patient to be removed from the study (i.e., due to an adverse event, insufficient improvement and required therapy).
- The patient requested to be withdrawn from the study.

A patient who was prematurely withdrawn from study during treatment was to return to the investigator's office within 48 hours after the last dose for post-treatment evaluation procedures (evaluation was to be made prior to the institution of any new therapeutic modality) and bacteriologic evaluations. At that time, the 4 to 6 Week Follow-up Visit evaluations were to be performed.

Medical Officer's Comment: Handling of patients who were removed from the study differed in this study as compared to the Astra-Merck studies 126 and 127 in that an eradication assessment was to be to be performed within 28 to 42 days in patients who were withdrawn from the study. This study design difference would tend to improve the results of the intent-

to-treat analysis as compared with the Astra-Merck studies 126 and 127 as fewer patients were to be assumed eradication failures.

OTHER STUDY DESIGN FEATURES

Patients were not allowed to have taken bismuth preparations or antibiotics at anytime within six weeks or proton pump inhibitors within four weeks prior to the start of the study and patients were instructed not to take any anti-ulcer or ulcerogenic medications, bismuth preparations, antimicrobials (i.e., metronidazole, amoxicillin, tetracycline, clarithromycin, azithromycin), aspirin, or NSAIDS during the study. In order to document compliance with the treatment regimen, patients were instructed to return the study drug containers at the Post-treatment Visit. If the patient was lost to follow-up, an estimated stop date of the study medication was recorded. In addition, it was recorded if the patient missed more than three consecutive days of study medication.

DIAGNOSTIC METHODS

The number of biopsies (N = 7) and diagnostic tests performed were similar to those used for studies 126 and 127.

EFFICACY ASSESSMENTS

The assessment of *H. pylori* eradication was similar to Astra-Merck studies 126 and 127 and consistent with the FDA Draft DAIDP Review Criteria: *Helicobacter pylori*-Associated Duodenal Ulcers (4/96) Document. Secondary efficacy variables included changes from baseline in signs and symptoms and histology variables, and ulcer incidence rates at the 4 to 6 Week Follow-up Visit. If the patient had a duodenal ulcer or duodenal erosion(s) at the follow-up exam, ulcer incidence was considered present. Susceptibility was assessed using the Etest and agar dilution.

SAMPLE SIZE DETERMINATIONS

225 patients (approximately 112 patients in each treatment group) were to be enrolled to obtain 180 patients (90 per treatment group) eligible for inclusion in the analysis of *H. pylori* eradication at the 4 to 6 Week Follow-up Visit. This assumed that approximately 80% of the enrolled patients would be eligible to be included in the analysis. This sample size provided greater than a 95% power for the detection of significant differences between treatment groups in *H. pylori* eradication rates at the 0.05 (2-tailed) level, assuming the *H. pylori* eradication rate was 80% for the C+A+O treatment group and 50% for the C+A treatment group.

Medical Officer's Comments: It appears that the analysis on which the study was powered was the per-protocol analysis. It should be noted that the FDA Draft DAIDP Review Criteria: Helicobacter pylori-Associated Duodenal Ulcers (4/96) Document and subsequent H. pylori guidance documents recommend that the "Modified Intent-to-treat" analysis be used as primary. Nevertheless, this study was "overpowered" as compared with Astra-Merck 126 and 127 studies.

AMENDMENTS

The original protocol was amended twice during the study. All 217 patients were randomized under Amendment #1 of the protocol.

- Amendment #1 (May 28, 1996)
- A follow-up endoscopy was added for those patients who prematurely discontinued the study drug therapy for any reason.
- The Four to Six Week Follow-up Visit was further defined as occurring within days after the last dose of study medication was taken.
- Amendment #2 (January 13, 1997)
- The number of participating investigative sites was increased by ten, as a result, the sample size increased from

EVALUABILITY CRITERIA/STATISTICAL METHODS

Three populations were defined for purpose of analysis:

- The All Enrolled Patients population was to be defined as all patients who took at least one dose of study medication
- The Intent-To-Treat population excluded patients with no confirmed evidence of *H. pylori* pretreatment, patients with a documented duodenal ulcer or duodenal erosion(s) present on the pretreatment endoscopy, patients with no confirmed history of duodenal ulcer, and patients who did not take any study medication
- The Per-Protocol population included all the patients who met the evaluability criteria.

Patients whose *H. pylori* eradication status was indeterminate at the 4 to 6 Week Follow-up Visit were excluded from the per-protocol analysis; however, they were included in the intent-to-treat analysis as bacteriologic failures (*H. pylori* status defined as positive).

Per-Protocol Analysis Evaluability Criteria

Medical Officer's Comment: In the original protocol, the evaluable patient population simply states that efficacy data will be analyzed for the evaluable (per protocol) population and that this includes only patients with no major protocol violations. Nevertheless, the study report states the following with regard to evaluability for the per-protocol analysis:

The sponsor's per-protocol patient population included those patients classified as "evaluable" and "evaluable with variation." The "evaluable" category included patients who fulfilled the protocol criteria, while the "evaluable with variation" category included patients who varied from the protocol; however, the variations were considered to not affect the eligibility of the patient for the analysis.

All of the following eligibility criteria must have been satisfied for a patient to be considered evaluable for the per-protocol efficacy analysis:

- The patient did not have an active duodenal ulcer, gastric ulcer, duodenal erosions, or erosive esophagitis, as confirmed by endoscopy within 14 days pretreatment.
- The patient had a history of duodenal ulcer, demonstrated by endoscopy or upper GI

radiogram, within the past 5 years.

- The patient had a positive culture or at least two of the following tests positive for *H. pylori* within 14 days pretreatment: CLOtest, culture, or histology.
- The patient had an endoscopy with biopsies performed 28 to 42 days (4 to 6 weeks) after the last dose. Evaluable patients for negative *H. pylori* status had at least two of the following tests negative for *H. pylori* and none positive: CLOtest, culture, or histology. Evaluable patients for positive *H. pylori* status had at least one of the following tests positive for *H. pylori*: CLOtest, culture, or histology.
- No interfering therapeutic procedures were performed from study drug administration through the follow-up visit, unless the patient was a failure.
- The patient did not take any bismuth preparations or antibiotics within six weeks prior and no proton pump inhibitors within four weeks prior to study drug administration up through the follow-up visit.
- The patient took at least 75% of the prescribed doses of each study medication and did not miss more than 3 consecutive days of therapy.
- The patient did not receive prior treatment for *H. pylori* eradication with a drug combination including clarithromycin.
- The patient prematurely discontinued study drug due to an adverse event and the 4 to 6 Week Follow-up Visit *H. pylori* status was indeterminate. The patient was evaluable as a failure (*H. pylori* status defined as positive).

Patients with acceptable variations from the evaluability criteria were considered "evaluable with variation". Acceptable variations included:

- The patient had a history of duodenal ulcer, demonstrated by endoscopy or upper GI radiogram, within the past 6 years, or the patient had a history of documented duodenal erosions within the past 6 years and a documented duodenal ulcer prior to that time.
- The patient had a positive culture or at least two of the following tests positive for *H. pylori* status within 21 days pretreatment: CLOtest, culture, or histology.
- The patient had a positive CLOtest, culture, or histology at any time post-treatment and the patient was otherwise not evaluable for the 4 to 6 Week Follow-up Visit.
- The patient had an endoscopy with biopsies performed 25 to 27 days after the last dose or greater than 42 days after the last dose, and at least two of the following tests were negative for *H. pylori* status: CLOtest, culture, or histology.
- The patient did not have more than 5 days of treatment with bismuth preparations, systemic antibiotics and/or proton pump inhibitors within four weeks prior to study drug administration, but the pretreatment culture was positive or at least two of the following tests were positive for *H. pylori*: CLOtest, culture, or histology.
- The patient received bismuth preparations or systemic antibiotics and/or proton pump inhibitors from study drug administration up through the follow-up visit and at least one of the post-treatment *H. pylori* tests (CLOtest, culture, histology) was positive.

Medical Officer's Comment: These criteria for the per-protocol analysis are consistent with the DAIDP [Draft] Evaluability recommendations. However, the Division's guidance is

more specific with regards to the handling of patients who dropout due to an adverse event. In those cases where the AE is related to the study drug or primary disease process, these patients are considered "evaluable failures" in the per-protocol analysis. In those cases where the AE is not related, they are considered non-evaluable in the per-protocol analysis.

Intent-to-Treat Patient Population

For patients not included in the per-protocol analysis, the following criteria must have been satisfied for the patient to be included in the intent-to-treat data set.

- The patient did not have an active duodenal ulcer, gastric ulcer, duodenal erosions, or erosive esophagitis, as confirmed by endoscopy within 14 days pretreatment.
- The patient had a history of duodenal ulcer, demonstrated by endoscopy or upper GI radiogram at any time pretreatment.
- The patient had a positive culture or had at least two of the following tests positive for *H. pylori* within 21 days pretreatment: CLOtest, culture, or histology.
- The patient took at least one dose of study medication.

Medical Officer's Comments: These criteria are generally consistent with the DAIDP [Draft] Evaluability guidelines, except for the requirement that patients had to have taken at least one dose of study medication to be included in the population.

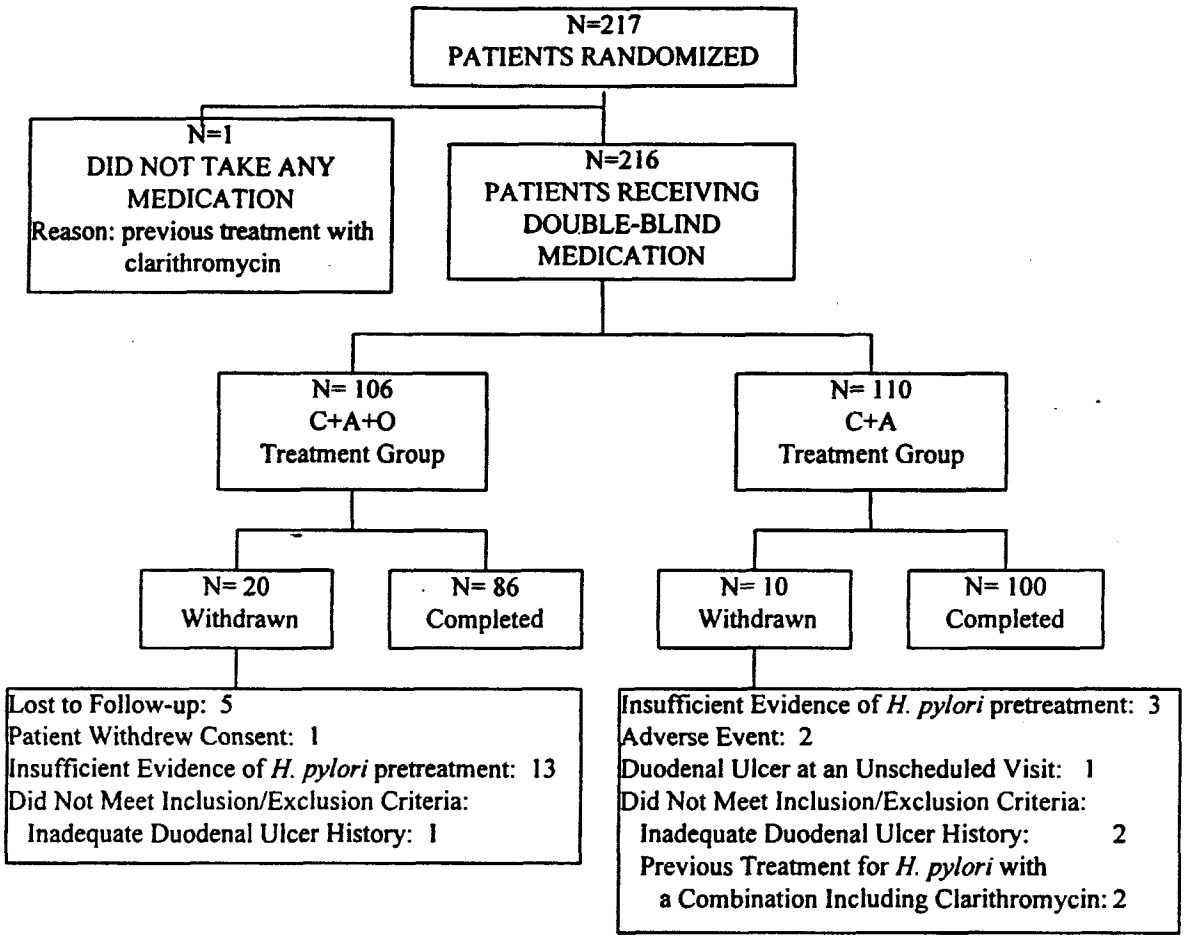
RESULTS

PATIENT DISPOSITION

There were 106 patients who received C+A+O, while 110 of the patients received C+A. Figure 4 outlines the disposition of all randomized patients.

APPEARS THIS WAY
ON ORIGINAL

Figure 4: Disposition of Patients



Statistical Reviewer's Comment: A significantly higher number of triple therapy patients were withdrawn from the study, 20 versus 10 (p=0.049 using Fisher's exact test). The difference is mostly due to two factors: (1) more triple therapy patients were lost to follow-up, 5 versus 0, and (2) more triple therapy patients were H. pylori negative at baseline, 13 versus 3.

ITT results discussed below may be just the least bit conservative, as those patients lost to follow-up were included as treatment failures in the ITT analysis; this will lower the eradication rate observed in the triple therapy arm but does not change the rate observed in the antibiotic alone arm.

H. pylori negative patients were excluded from both the ITT and per protocol analyses, hence more tripe therapy patients were excluded from these analyses.

Patients who did not complete the study are listed in Table 43.

Table 43: Patients Who Did Not Complete the Study (C+A+O Treatment Group)

Reason for Withdrawal	Patient #	Age	Sex	Investigator
Lost to Follow-up (N = 5)	143	52	M	Simmons
	289	40	F	Lanza
	292	34	M	Silverman
	348	29	F	Kogut
	440	25	M	Lanza
Patient Withdrew Consent (N = 1)	276	40	F	Reymunde
Insufficient Evidence of *H. pylori* Pretreatment	118	50	F	Lanza
(N = 13)	127	47	M	Rubin
	140	59	M	Simmons
	151	39	F	Aaronson
	191	77	M	Wruble
	210	33	M	Martin
	227	42	M	Reymunde
	239	58	M	Reymunde
	251	29	M	Cutler
	258	47	M	Reymunde
	260	26	F	Loludice
	306	73	M	Simmons
	404	60	M	Loludice
Inadequate Duodenal Ulcer History (N = 1)	296	46	M	Cave

Patients Who Did Not Complete the Study (C+A Treatment Group)

Reason for Withdrawal	Patient #	Age	Sex	Investigator
Insufficient Evidence of *H. pylori* Pretreatment	211	41	F	Martin
(N = 3)	263	21	F	Loludice
	349	44	M	Kogut
Adverse Event (N = 2)	228	73	F	DeMicco
	373	51	F	Wruble
Duodenal Ulcer at Unscheduled Visit (N = 1)	389	65	M	Caos
Inadequate Duodenal Ulcer History (N = 2)	224	65	F	Reymunde
	265	72	F	Vakil
Previous Treatment for *H. pylori* with a	237	59	F	Reymunde
Combination Containing Clarithromycin (N = 2)	281	52	F	Attar

In addition, two of the 100 patients in the C+A treatment group who completed the 4 to 6 Week Follow-up Visit did not have bacteriologic tests performed at that visit (Patient #128 and Patient #226).

STUDY DRUG COMPLIANCE

Four percent (8/216) of the patients who were enrolled in the study prematurely discontinued study drug. The primary reason for discontinuation from study drug therapy was adverse event. The reasons for premature discontinuation from the study drug are summarized in Table 44. Of the five patients who discontinued study drug therapy due to an adverse event, two were not evaluable due to "insufficient evidence of *H. pylori* pretreatment." The other three patients were included in the analysis as evaluable bacteriologic failures (*H. pylori* status was positive) and assigned an indeterminate response for ulcer incidence.

Table 44: Patients Who Prematurely Discontinued Study Drug Therapy

Primary Reason for Discontinuation	Number of Patients		
	C+A+O	C+A	Total
Adverse Event	1	4	5 (2.3%)
Lost to Follow-up	3	0	3 (1.4%)
Total	4	4	8 (3.7%)

Drug compliance for the eight patients who prematurely discontinued taking study medication is presented in Table 45.

Table 45: Amount of Study Drug Taken By Patients Who Prematurely Discontinued Study Drug Therapy

Patient No.	Number of Tablets/Capsules Taken (%)		
	Clarithromycin	Amoxicillin	Omeprazole/Placebo
143@			
228	5 (25%)	10 (25%)	5 (25%)
233	9 (45%)	18 (45%)	10 (50%)
276	12 (60%)	24 (60%)	12 (60%)
281	6 (30%)	12 (30%)	6 (30%)
292@			
348@			
373	5 (25%)	10 (25%)	5 (25%)
Mean	7.4 (37%)	14.8 (37%)	7.6 (38%)

@ Patient was lost to follow-up and no drug accountability was available.

PROTOCOL DEVIATIONS

Table 46 shows the distribution of the number of patients who were enrolled with a deviation by the specific selection criteria. If the variation was considered to not compromise the outcome of the study or the safety of the patient, the patient may have been approved for study participation.

Table 46: Significant Deviations - Selection Criteria

Selection Criteria	Number of Patients@		
Inclusion Criteria	C+A+O	C+A	Total
#1: Male or female ≥18 years of age	0	0	0
#2: No active duodenal ulcer or duodenal erosion present at pretreatment	0	0	0
#3: A qualifying ulcer history	10	14	24
#4: A positive urease test (CLOtest)	1	2	3
#5: Acceptable health	0	0	0
#6: At no risk of pregnancy	0	0	0
#7: Signed an informed consent	0	0	0
Exclusion Criteria			
#8: Evidence of active duodenal ulcer or duodenal erosions	1	2	3
#9: Prior administration of bismuth preparations or antibiotics	2	1	3
#10: Prior administration of proton pump inhibitor	1	2	3
#11: Requirement of anti-ulcer maintenance therapy	0	1	1
#12: Concomitant administration of diazepam, phenytoin, warfarin, digoxin, disulfiram, theophylline, or carbamazepine	0	0	0
#13: Concomitant administration of terfenadine, pimozide, astemizole, or cisapride	0	0	0
#14: Evidence of gastric ulcer, gastric malignancy, pyloric obstruction, erosive esophagitis, esophageal stricture requiring dilation, fresh clot, active bleeding or perforated ulcer(s)	1	0	1
#15: History of gastric surgery or vagotomy for ulcer disease	0	1	1
#16: History of hypersensitivity or allergic reaction to macrolides, penicillins, or benzimidazole compounds	1	1	2
#17: Participation in a drug study within 8 weeks prior to study start	0	1	1
#18: Prior treatment for *H. pylori* with a combination including clarithromycin	2	4	6
#19: Prior treatment for *H. pylori* within 3 months prior to study start	1	0	1
#20: Evidence of alcohol abuse, illegal drug use or drug abuse	0	0	0
#21: History of uncontrolled clinically significant cardiovascular, pulmonary, renal, hepatic, metabolic, gastrointestinal, neurologic, immunologic or endocrine disease, malignancy, or other abnormality likely to complicate the evaluation of study treatment	1	0	1
#22: Calculated creatinine clearance <40 ml/min	0	0	0
#23: Evidence of concomitant disease related to ulcer	1	0	1
#24: Requirement of chronic pre-existing NSAIDs, steroids, anticoagulants, anticholinergics, antidepressants, salicylates, or antineoplastic agents	8	2	10
#25: Hospitalized	0	0	0
#26: A disorder that would contraindicate the procedures	0	0	0
TOTAL	30	31	61

@ If more than one selection criteria was deviated from by a patient, that patient is included in each selection criteria deviated from.

Six patients developed withdrawal criteria during study participation and remained in the study. One patient did not take at least 75% of each of the study medications and five patients took confounding medications during the time from the study drug administration up through the 4 to 6 Week Follow-up Visit. All six patients were included in the intent-to-treat analysis. Table 47 shows the number of patients who developed withdrawal criteria and remained in the study.

Table 47: Significant Deviations - Patients Who Developed Withdrawal Criteria and Remained in the Study

Patients who took confounding medications:

Patient Number	Age/ Sex	Investigator	Confounding Medication	Start Date@	Reason for Use
C+A+O					
169	82M	Barreiro	Ciprofloxacin	Study Day 27 (17)	Diarrhea
171	27M	Barreiro	Erythromycin	Study Day 22 (12)	Allergic Reaction
C+A					
152	50F	Rosenberg	Prilosec	Study Day 32 (22)	Abdominal Pain
174	40F	Levenson	Ciprofloxacin	Study Day 48 (38)	Cholecystitis
361	70F	Shah	Ciprofloxacin	Study Day 20 (10)	Urinary Tract Infection

Patient who took less than minimum therapy:

Patient Number	Age/ Sex	Investigator	Clarithromycin Tablets Taken	Amoxicillin Tablets Taken	Omeprazole Capsules Taken
332	47F	Cline	20 (100%)	40 (100%)	14 (70%)

@ Days post-treatment shown in parenthesis.

The numbers of patients in each analysis population is shown in Table 48

Table 48: Disposition of Patients by Data Set

	C+A+O	C+A
Total Enrolled	106	110
Patients Included in the Intent-to-Treat Efficacy Analysis:	**84**	**99**
Patients Excluded from the Intent-to-Treat Efficacy Analysis:		
Insufficient evidence of *H. pylori* pretreatment	21	9
Duodenal ulcer/duodenal erosion(s) present pretreatment	1	2
Patients Included in the Per-Protocol Efficacy Analysis:	**69**	**94**
Patients Excluded from the Per-Protocol Efficacy Analysis:		
Insufficient evidence of *H. pylori* pretreatment	21	9
No follow-up exam	5	1
Inadequate duodenal ulcer history	5	3
Confounding medications	3	0
Duodenal ulcer/duodenal erosion(s) present pretreatment	1	2
Less than minimum therapy	1	0
Mistiming of pretreatment exam	1	0
Prior treatment for *H. pylori* with a combination including clarithromycin	0	1

NOTE: Two patients (1 C+A+O, 1 C+A) were assigned two reasons for exclusion from the analysis: inadequate ulcer history and mistiming of follow-up visit. These patients are included in the table as "inadequate ulcer history;" this reason was considered primary since it was a violation of the selection criteria.

NOTE: Five patients were prematurely discontinued due to an adverse event; two of them had insufficient evidence of *H. pylori* pretreatment, therefore these patients were excluded from the per-protocol and intent-to-treat analyses. The other three patients were included in the per-protocol and intent-to-treat analyses as evaluable failures.

Statistical Reviewer's Comment: A significantly lower number of triple therapy patients were included in both the intent-to-treat and per-protocol analysis (p-values of 0.04 and 0.0008, respectively). Much of the difference can be attributed to the greater number of triple therapy patients who had insufficient evidence of H. pylori at baseline, 21 versus 9. The reason for this baseline imbalance is unclear.

Medical Officer's Comment: Table 48 suggests that only 8 patients were withdrawn from the per-protocol analysis because of an inadequate duodenal ulcer history. However, Table 46 suggests that 24 patients were allowed in the study who did not have a "qualifying ulcer history". During a teleconference on April 16th, 1998 the sponsor stated that this difference existed because there were 16 patients who were included in the analysis because their ulcer was documented to have occurred 5-6 years prior to the study, and hence, were considered "evaluable with variation". Therefore, only 8 patients were excluded by the sponsor from the per-protocol efficacy analysis. The Medical Officer requested that eradication rates be

calculated for patients who had a history of DU disease within 5 years of entering the study (See Table 49 below.) Among the 16 patients who had ulcers documented between 5 and 6 years prior to the study, 3 were excluded from the per-protocol analysis due to 1) duodenal ulcer/duodenal erosions present at pretreatment (ID # 209), insufficient evidence of H. pylori pretreatment (ID # 263), and no follow-up exam (ID # 292).

DEMOGRAPHICS

There were no differences between the treatment regimens in either gender, age, race, or weight. There were also no statistically significant differences between treatment groups with respect to the mean number of previous duodenal ulcer occurrences (1.94 for the C+A+O treatment group and 1.73 for the C+A treatment group), alcohol use, or tobacco use.

EFFICACY RESULTS

Per-protocol and intent-to-treat *H. pylori* eradication rates are presented in table 49 and table 50 for patients regardless of pre-treatment susceptibility status and for patients with clarithromycin susceptible strains pretreatment, respectively. Table 49 includes the per-protocol eradication rates for patients who had a duodenal ulcer history within 5 years of follow-up, a duodenal ulcer history between 5 and 6 years prior to admission, and a duodenal ulcer history longer than 6 years.

Table 49: Global Eradication at the 4 to 6 Week Follow-up Visit

	C+A+O	C+A	P-value
Per-protocol	62/69 (90%)	31/93 (33%)	<0.001*
[CI]	[80.2, 95.8]	[23.9, 43.9]	
PP - DU hx within 5 years	58/65 (89%)	27/85 (32%)	
PP - DU hx between 5 and 6 years	4/4 (100%)	4/9 (44%)	
PP - DU hx longer than 6 years	3/5 (75%)	0/3 (0%)	
Intent-to-Treat	70/84 (83%)	32/99 (32%)	<0.001*
[CI]	[73.6, 90.6]	[23.3, 42.5]	

* Indicates statistical significance (2-tailed) at the 0.05 level.
NOTE: P-value was calculated using Fisher's exact test and the confidence interval was calculated by exact binomial method.

APPEARS THIS WAY
ON ORIGINAL

Table 50: Global Eradication at the 4 to 6 Week Follow-up Visit for Patients with Pretreatment Clarithromycin Susceptible Isolates			
	C+A+O	C+A	P-value
Per-protocol	56/59 (95%)	26/68 (38%)	<0.001*
[CI]	[85.9, 98.9]	[26.7, 50.8]	
Intent-to-Treat	64/71 (90%)	26/73 (36%)	<0.001*
[CI]	[80.7, 95.9]	[24.7, 47.7]	

* Indicates statistical significance (2-tailed) at the 0.05 level.
NOTE: P-value was calculated using Fisher's exact test and the confidence interval was calculated by exact binomial method.

Medical Officer's Comments: From Table 49, it is clear that if only patients who had duodenal ulcer disease documented within 5 years were included (as per the original protocol), there would not be any major changes in the per-protocol eradication rates.

Statistical Reviewer's Comment: The applicant is requesting that their triple therapy regimen be indicated for patients with either active DU or a history of DU in the past 5 years. Since current labels for other drugs in this area only include patients with a history of DU in the past year (or patients with active DU), the statistical reviewer examined eradication rates by ulcer history status for each treatment group in more detail. The sponsor's ulcer history categories were used: < 1 year, 1 - 3 years, 3 - 5 years, and > 5 years.

Tables 51 and 52 present eradication rates by treatment group and ulcer history for the per-protocol and intent-to-treat populations, respectively. Within treatment groups, rates are fairly consistent across the different ulcer history categories (i.e., rates for patients with a < 1 year history of DU do not appear very different from rates for patients with a < 5 year history). The question remaining is whether eradication of H. pylori for patients with a 1 - 5 year history of DU has been shown to translate into clinical benefit.

Table 51: Global Eradication at the 4 to 6 Week Follow-Up Visit by Ulcer History (Per-Protocol)

Ulcer History	C+A+O (N=69)	C+A (N=93)
< 1 year ago	11/14 (78.6%)	8/16 (50.0%)
1 - 3 years ago	9/11 (81.8%)	6/25 (24.0%)
3 - 5 years ago	18/19 (94.7%)	11/32 (34.4%)
> 5 years ago	24/25 (96.0%)	6/20 (30.0%)

Table 52: Global Eradication at the 4 to 6 Week Follow-Up Visit by Ulcer History (Intent-to-Treat)

Ulcer History	C+A+O (N=84)	C+A (N=98)*
< 1 year ago	11/14 (78.6%)	8/16 (50.0%)
1 - 3 years ago	11/15 (73.3%)	7/27 (25.9%)
3 - 5 years ago	19/20 (95.0%)	11/32 (34.4%)
> 5 years ago	29/35 (82.9%)	6/23 (26.1%)

*One patient did not have ulcer history data.

Statistical Reviewer's Comment (continued): The FDA's Division of Scientific Investigations (DSI) found that one of the study centers was not in compliance (investigator: Dr. Reymunde). Upon the recommendation of DSI, efficacy was reexamined after excluding the data from this site. Results are very similar (see below).

Twenty-six patients were enrolled at Dr. Reymunde's site. When these patients are excluded from the per-protocol analysis, the rate for the triple therapy arm is 54/60, or 90% (95% exact confidence interval [79%, 96%]) and the rate for the antibiotic alone arm is 26/83, or 31% (95% exact confidence interval [22%, 42%]). This difference is statistically significant ($p<0.001$ using Fisher's exact test). When these patients are excluded from the intent-to-treat analysis, the rate for the triple therapy arm is 62/74, or 84% (95% exact confidence interval [73%, 91%]) and the rate for the antibiotic alone arm is 27/88, or 31% (95% exact confidence interval [21%, 41%]). This difference is statistically significant ($p<0.001$ using Fisher's exact test).

The diagnostic correlation among the three endoscopic *H. pylori* tests used are shown in Table 53 for the pre-treatment visit and the eradication visit.

Table 53: Percent Agreement Among Endoscopic *H. pylori* Tests

Pre-Treatment	Histology vs. Culture	Histology vs. CLOtest	CLOtest vs. Culture
Overall	197/212 (93%)	183/215 (85%)	166/213 (78%)
C+A+O	98/105 (93%)	84/106 (79%)	76/105 (72%)
C+A	99/107 (93%)	99/109 (91%)	90/108 (83%)

Week 8	Histology vs. Culture	Histology vs. CLOtest	CLOtest vs. Culture
Overall	168/180 (93%)	172/181 (95%)	162/179 (91%)
C+A+O	80/82 (98%)	83/84 (99%)	80/83 (96%)
C+A	88/98 (90%)	89/97 (92%)	82/96 (85%)

A summary of *H. pylori* status at the pre-treatment and post-treatment visit is presented in Table 54 and 55, respectively.

Table 54: Summary of *H. pylori* Infection Status by Diagnostic Tests at the Pretreatment (All Available Data)

Culture	Histology	CLOtest	Patient Status@	Number of Patients	
				C+A+O	C+A
Three Tests Available					
-	-	-	Not Evaluable	0	0
-	-	+	Not Evaluable	21	7
-	+	-	Not Evaluable	0	0
-	+	+	Evaluable	7	8
+	-	-	Evaluable	0	0
+	-	+	Evaluable	0	0
+	+	-	Evaluable	1	2
+	+	+	Evaluable	76	90
Two Tests Available					
-	-	N/A	Not Evaluable	0	0
-	+	N/A	Not Evaluable	0	0
-	N/A	-	Not Evaluable	0	0
-	N/A	+	Not Evaluable	0	1
+	-	N/A	Evaluable	0	0
+	+	N/A	Evaluable	0	0
+	N/A	-	Evaluable	0	0
+	N/A	+	Evaluable	0	0
N/A	-	-	Not Evaluable	0	0
N/A	-	+	Not Evaluable	0	1
N/A	+	-	Not Evaluable	0	0
N/A	+	+	Evaluable	1	1
One Test Available					
-	N/A	N/A	Not Evaluable	0	0
+	N/A	N/A	Evaluable	0	0
N/A	-	N/A	Not Evaluable	0	0
N/A	+	N/A	Not Evaluable	0	0
N/A	N/A	-	Not Evaluable	0	0
N/A	N/A	+	Not Evaluable	0	0
Zero Test Available					
N/A	N/A	N/A	Not Evaluable	0	0

N/A = Not available

@ Using the FDA Draft DAIDP Review Criteria: *Helicobacter pylori*-Associated Duodenal Ulcers (4/96)

Assigned a bacteriologic response of Indeterminate

APPEARS THIS WAY
ON ORIGINAL

Table 55: Summary of *H. pylori* Infection Status by Diagnostic Tests at the 4 to 6 Week Follow-up (All Available Data)

Culture	Histology	CLOtest	Patient Status@	Number of Patients	
				C+A+O	C+A
Three Tests Available					
-	-	-	Eradicated	76	33
-	-	+	Persistence	1	3
-	+	-	Persistence	0	2
-	+	+	Persistence	2	8
+	-	-	Persistence	0	0
+	-	+	Persistence	0	0
+	+	-	Persistence	0	3
+	+	+	Persistence	3	47
Two Tests Available					
-	-	N/A	Eradicated	0	0
-	+	N/A	Persistence	0	0
-	N/A	-	Eradicated	1	0
-	N/A	+	Persistence	0	0
+	-	N/A	Persistence	0	0
+	+	N/A	Persistence	0	2
+	N/A	-	Persistence	0	0
+	N/A	+	Persistence	0	0
N/A	-	-	Eradicated	1	1
N/A	-	+	Persistence	0	0
N/A	+	-	Persistence	0	0
N/A	+	+	Persistence	1	0
One Test Available					
-	N/A	N/A	Not Evaluable#	0	1
+	N/A	N/A	Persistence	0	0
N/A	-	N/A	Not Evaluable#	0	0
N/A	+	N/A	Persistence	0	0
N/A	N/A	-	Not Evaluable#	1	0
N/A	N/A	+	Persistence	0	0
Zero Test Available					
N/A	N/A	N/A	Not Evaluable#	20	10

N/A = Not available

@ Using the FDA Draft DAIDP Review Criteria: *Helicobacter pylori*-Associated Duodenal Ulcers (4/96)

Assigned a bacteriologic response of Indeterminate

Medical Officer's Comment: The number of "false negative" CLOtest results as compared with either culture or histology at the follow-up visit was less than those seen in the Astra-Merck 126 and 127 studies (6% and 7%, respectively).

There were 10 patients with discordant test results at the 4 to 6 Week Follow-up Visit that warranted reassessment by the sponsor. These 10 patients were the only patients who had one bacteriologic response positive and the other two test results negative: eight patients were histology positive, culture negative, and CLOtest negative and two patients were histology

negative, culture negative, and CLOtest positive. In a blinded fashion the pathologist confirmed the histology results for all 10 patients. The re-read results replaced the original histology results for final analysis. The histology results of 4 patients were changed from negative to positive, 5 had no change in their histology results, and 1 had the histology result change from positive to indeterminate as it was determined that bacteria were present but unlikely to be *H. pylori* in this patient.

Medical Officer's Comments: Since this re-analysis was done blinded, it is acceptable.

RESOLUTION OF SYMPTOMS

APPEARS THIS WAY
ON ORIGINAL

Symptom resolution results are outlined in Table 56. No statistical differences were noted between treatment groups.

Table 56: Resolution and Resolution/Improvement of Baseline Signs/Symptoms At Post-treatment (Per-Protocol Population)

	C+A+O	C+A	P-value
Day Time Abdominal Pain			
Resolution	20/33 (61%)	35/52 (67%)	0.642
Resolution/Improvement	29/33 (88%)	45/52 (87%)	>0.999
Night Time Abdominal Pain			
Resolution	23/32 (72%)	34/43 (79%)	0.587
Resolution/Improvement	31/32 (97%)	39/43 (91%)	0.386
Epigastric Pain/Burning			
Resolution	24/37 (65%)	33/53 (62%)	0.828
Resolution/Improvement	32/37 (86%)	42/53 (79%)	0.417
Nausea			
Resolution	12/17 (71%)	18/28 (64%)	0.752
Resolution/Improvement	14/17 (82%)	19/28 (68%)	0.488
Vomiting			
Resolution	5/5 (100%)	8/10 (80%)	0.524
Resolution/Improvement	5/5 (100%)	9/10 (90%)	>0.999

Resolution = Change from present at pretreatment to absent at the Post-treatment Visit
Resolution/Improvement = A decrease in severity of the sign/symptom from pretreatment to the Post-treatment Visit.

ULCER INCIDENCE

Ulcer incidence at follow-up is summarized in Table 57. There were no statistically significant differences between treatments for either the per-protocol or intent-to-treat patient populations.

Table 57: Ulcer Incidence Rates at the 4 to 6 Week Follow-up Visit			
	C+A+O	C+A	P-value
Per-protocol	4/68 (6%)	8/92 (9%)	0.560
[CI]	[1.6, 14.4]	[3.8, 16.4]	
Intent-to-Treat	5/84 (6%)	9/99 (9%)	0.580
[CI]	[2.0, 13.3]	[4.2, 16.6]	
NOTE: P-value was calculated using Fisher's exact test and the confidence interval was calculated by exact binomial method.			

SAFETY RESULTS

The number of patients who had events that led to patients to be discontinued are outlined in Table 58.

Table 58: Listing of Adverse Events Leading Patients to Prematurely Discontinue Study Medication

Pt. #	Age/ Sex	Group	# of Days@	Description	COSTART	Body System	Other Action Taken
228	73F	C+A	3	Diarrhea	Diarrhea	Digestive	Medication Self-Prescribed
233	76M	C+A	6	Burning in Stomach/Upset Stomach	Abdominal Pain/ Dyspepsia	Digestive	None
				Diarrhea	Diarrhea	Digestive	
276	40F	C+A+O	6	Chest Pain, R/O Pectoralis Angina	Angina Pectoris	Cardiovascular	Hospitalized
281	52F	C+A	3	Sick to Her Stomach	Abdominal Pain	Digestive	None
373	51F	C+A	4	Itching Restlessness	Pruritis Nervousness	Skin & Appendages Nervous	None

@ = number of days on study medication

Three patients experienced alterations in laboratory test results that were considered "probably" related to study medication by the investigator; however, none led to the withdrawal of study medication or an alteration in the patients' concurrent medication use.

REVIEWERS' CONCLUSIONS FOR ABBOTT STUDY M96-446

This was a well conducted, randomized, clinical trial which convincingly demonstrated the superiority of triple therapy (O + A + C) over antibiotics alone (A + C) when given for 10 days with twice daily dosing. The lower bound of the 95% confidence interval of the point estimate for triple therapy using the ITT analysis was 74%, much more than the 60 percent threshold as suggested by the Division.

In addition, multiple interesting observations were made:

- *There did not appear to be any significant difference in eradication rates if only patients with a history of ulcers within 5 years were included.*
- *Eradication rates were similar for patients with a < 1 year history of DU and patients with a < 5 year history of DU.*
- *The sensitivity of CLOtest at the follow-up as compared with culture (alone) and histology (alone) was 6% (3/53) and 7% (5/66), respectively. In general, there was good agreement between the three endoscopic tests at the pre-treatment and post-treatment visits.*
- *The evaluation of symptom resolution did not suggest any significant difference between treatment arms when evaluating abdominal pain, epigastric pain/burning, nausea, or vomiting.*
- *There was no significant difference in ulcer incidence rates at 4-6 weeks post-treatment between the triple therapy and antibiotic alone arms. However, the results of this analysis should be suspect because ulcer incidence was assessed at different time points in different patients.*
- *Few patients experienced adverse events that led to premature discontinuation (4 antibiotic alone and 1 triple therapy).*

INTEGRATED SAFETY REVIEW

DEMOGRAPHICS

The demographics of the study populations for the pivotal studies are shown in Table 59.

Table 59: Demographics of Study Population in Pivotal Studies of the O 20 bid + A 1000 bid + C 500 bid Regimen (Astra Merck Studies 126, 127 and Abbott Study M96-446 Only

	O 20 bid + A 1000 bid + C 500 bid (n=274) n(%)	A 1000 bid + C 500 bid (n=284) n(%)
Gender		
Male	174 (64%)	177 (62%)
Female	100 (36%)	107 (38%)
Age (years)		
<35	53 (19%)	37 (13%)
35-44	75 (27%)	67 (24%)
45-54	67 (24%)	76 (27%)
55-65	41 (15%)	68 (24%)
>65	38 (14%)	36 (13%)
Mean Age	47.0	49.0
S.D.	14.0	13.0
Median	46	49
Range		
Race		
Caucasian	179 (65%)	176 (62%)
Black	62 (23%)	71 (25%)
Asian	8 (3%)	8 (3%)
Other	25 (9%)	29 (10%)

ADVERSE EVENTS

Adverse events were graded as mild, moderate, or severe for all studies. The Astra-Merck studies used a modified version of WHOART to code adverse events and the Abbott Study used COSTART for adverse event coding. The number and percentage of patients with at least one clinical or laboratory adverse event is listed in Table 60.

Table 60: Number and Percentage of Patients with at Least One Clinical or Laboratory Adverse Event (AE) in Pivotal Studies of the O 20 bid + A 1000 bid + C 500 bid Regimen (Astra Merck Studies 126, 127 and Abbott Laboratories Study M96-446)

	Treatment Group	
	O 20 bid + A 1000 bid + C 500 bid n=274 n (%)	A 1000 bid + C 500 bid n=284 n (%)
Patients with at Least One Clinical AE	128 (46.7%)	134 (47.2%)
Patients with at Least One Drug Related Clinical AE	73 (26.6%)	79 (27.8%)
Patients with at Least One Serious Clinical AE	2 (0.7%)	2 (0.7%)
Patients with at Least One Drug Related Serious Clinical AE	0 (0.0%)	0 (0.0%)
Patients with at Least One Laboratory AE	14 (5.1%)	18 (6.3%)
Patients with at Least One Drug Related Laboratory AE	6 (2.2%)	5 (1.8%)
Patients with at Least One Serious laboratory AE	0 (0.0%)	0 (0.0%)
Patients with at Least One Drug Related Serious Laboratory AE	0 (0.0%)	0 (0.0%)

Drug Related is defined as any AE that is believed by the investigator to be Possibly or Probably Related to the drug.

The percentage of patients (>2%) with specific clinical adverse events (and relationship to study drugs) is listed in Table 61.

Table 61: Percent of Patients (≥2% in any treatment group) Who Had a Specified Clinical Adverse Event by Body System Category in Pivotal Studies of the O 20 bid + A 1000 bid + C 500 bid Regimen (Astra Merck Studies 126, 127 and Abbott Study M96-446)

Clinical Adverse Event by Body System	O 20 bid + A 1000 bid + C 500 bid n=274 % [% Drug Rel]	A 1000 bid + C 500 bid n=284 % [% Drug Rel]
Gastrointestinal System		
Diarrhea	13.9 [12.0]	13.7 [12.3]
Nausea	4.4 [2.6]	5.6 [2.8]
Abdominal Pain	4.0 [1.8]	3.9 [1.4]
Vomiting	2.9 [1.8]	1.8 [0.7]
Flatulence	1.8 [0.4]	2.8 [2.5]
Special Senses		
Taste Perversion	9.9 [9.9]	7.7 [7.4]
Central and Peripheral Nervous System		
Headache	6.6 [1.5]	4.9 [1.1]
Respiratory System		
Sinusitis	2.9 [0.0]	1.4 [0.0]
Respiratory Infection	2.6 [0.0]	2.8 [0.0]
Pharyngitis	2.2 [0.7]	1.8 [0.0]
Body as a Whole		
Back Pain	2.6 [0.0]	1.1 [0.0]
Psychiatric		
Insomnia	1.8 [0.0]	2.1 [1.8]

"% Drug Related" AEs appear as [X.X] in the table.
Drug Related is defined as any AE that is believed by the investigator to be Possibly or Probably Related to the study drug.

There were no clinically significant trends in AE by body system when evaluating for the effect of gender, race, or age.

LABORATORY ADVERSE EVENTS

Table 62 shows the percentage of patients (> 2% in any treatment group) who had laboratory adverse events by laboratory test for the pivotal studies.

Table 62:
Percent of Patients (≥2% in any treatment group) Who Had a Specified Laboratory Adverse Event by Laboratory Test in Pivotal Studies of the O 20 bid + A 1000 bid + Clarithromycin 500 bid Regimen (Astra Merck Studies 126, 127 and Study M96-446 Only)

Laboratory Test Laboratory Adverse Event	Number patients with test	O 20 bid + A 1000 bid + C 500 bid % [% Drug Rel]	Number patients with test	A 1000 bid + C 500 bid % [% Drug Rel]
CHEMISTRY				
GGT* increased	101	0.0 [0.0]	109	2.8 [1.8]
ALT (SGPT) increased	267	2.6 [1.9]	276	1.1 [0.7]
AST (SGOT) increased	267	2.2 [1.5]	276	1.4 [0.7]
URINALYSIS				
Microscopic Hematuria	166	0.0 [0.0]	167	3.0 [1.2]

"% Drug Related" AEs appear as [X.X] in the table.
Drug Related is defined as any AE that is believed by the investigator to be Possibly or Probably Related to the drug.
* GGT was routinely performed on subjects in Study M96-446 only.

DISCONTINUATIONS DUE TO ADVERSE EVENTS

There were 15 of 558 patients who experienced clinical adverse events that required discontinuation. One additional patient discontinued due to a laboratory adverse event. These patients are listed in Table 63. Most of these were possibly or probably related to study medication administration.

APPEARS THIS WAY
ON ORIGINAL

TABLE 63
Patients Discontinued from Study Due to Adverse Events (Clinical or Laboratory)
Astra Merck Studies 126, 127 and , Study M96-446)

Study no./ Alloc no.	Investigator	Gender	Age	Relative day of Onset	AE	Duration (Days)	Intensity	Drug Rel.	Serious	Study day discontinued	Action Taken
O 20 bid + A 1000 bid + C 500 bid											
126/ 6154	Gaddam	Male	59	11	SGOT increased	unknown	unknown	possible	no	Followed for 92 days	test drug stopped Day 15
				11	SGPT increased	unknown	unknown	possible	no		
127/ 6642	Safdi	Female	73	2	Fatigue	2	moderate	possible	no	4	test drug stopped Day 3
				2	Nausea	2	severe	probable	no		
127/ 6714	Silvers	Male	32	1	Abdominal Pain	5	severe	possible	no	7	test drug stopped Day 5
				1	Diarrhea	5	severe	probable	no		
				1	Nausea	5	severe	probable	no		
127/ 6623	Krause	Female	37	1	Diarrhea	<1	moderate	probable	no	64	test drug stopped Day 1
127/ 6592	Resnick	Female	39	1	Taste Perversion	unknown	severe	possible	no	16	test drug stopped Day 3
M96-446/ 276	Rey-munde	Female	40	6	Angina Pectoris	4	moderate	unlikely	yes	6	test drug stopped

TABLE 63 (cont.)
Patients Discontinued from Study Due to Adverse Events (Clinical or Laboratory)
Astra Merck Studies 126, 127 and Study M96-446)

Study no./ Alloc no.	Investigator	Gender	Age	Relative day of Onset	AE	Duration (Days)	Intensity	Drug Rel.	Serious	Study day discon tinued	Action Taken
A 1000 bid + C 500 bid											
126/ 6105	Barish	Female	44	30	Dyspepsia	still present when patient discon-tinued from the study	moderate	unlikely	no	36	none
126/ 6030	Maton	Female	59	2 2	Anxiety Nervousness	<1 <1	moderate moderate	probable probable	no no	2	test drug stopped Day 1
127/ 6535	Riff	Female	34	31	Abdominal Pain	unknown	severe	unlikely	no	42	none
127/ 6644	Safdi	Female	78	21	Pneumonia	28	moderate	unlikely	no	49	none
127/ 6553	Diamant	Female	79	4	Urticaria	7	moderate	probable	no	11	test drug stopped Day 7
127/ 6591	Resnick	Male	49	1 1	Nausea Vomiting	3 1	moderate mild	probable probable	no no	11	test drug stopped Day 3
M96-446/ 233	S.Sontag	Male	76	3 3 3	Abdominal Pain Diarrhea Dyspepsia	9 7 9	moderate mild moderate	probable probable probable	no no no	6	test drug stopped
M96-446/ 228	DeMicco	Female	73	2 2	Diarrhea Flatulence	3 3	severe mild	probable probable	no no	3	test drug stopped
M96-446/ 281	B. Attar	Female	52	1	Abdominal Pain	4	moderate	possible	no	3	test drug stopped
M96-446/ 373	Wruble	Female	51	2 2	Ner-vousness Pruritus	3 3	mild mild	probable probable	no no	4	test drug stopped

There were no cases of *C. difficile* colitits noted in the three pivotal U.S. studies.

SERIOUS ADVERSE EVENTS

In the pivotal studies there were 4 non-fatal serious AEs, none of which was related to study medication. Two patients received dual therapy, and two received triple therapy. All were unlikely related to study drug. None of the studies in the complete safety dataset had serious AEs or deaths that were thought to be related to the study medication.

LABORATORY EVALUATIONS

There were no clinically meaningful differences between treatment groups among the three U.S. pivotal studies when evaluating the mean changes from baseline to end of therapy for any of the laboratory tests evaluated.

In an effort to evaluate for "significant" changes in laboratory results while on treatment, the sponsor studied individual changes in patient laboratory values (baseline to end of therapy) according to predefined limits of change. There were no clinically meaningful differences between treatment groups among the three U.S. pivotal studies when evaluating changes from baseline outside predefined limits at the end of therapy.

REVIEWERS' CONCLUSIONS OF SAFETY

The 14 % incidence of diarrhea is fairly high as compared with the Lansoprazole triple therapy 2-week regimen. In the lansoprazole regimen only 7% of patients developed diarrhea.

Ten percent of omeprazole triple therapy patients developed taste disturbance and 7% developed headache. Nevertheless, the number of patients who discontinued due to an adverse event in the omeprazole 10-day triple therapy regimen was very low.

INTEGRATED EFFICACY REVIEW (INCLUDING COMBINATION RULE)

21 CFR 300.50 states that: "two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug." Two pre-NDA meetings with the sponsor were carried out to discuss this rule in the context of the sponsor's planned clinical development plan. Of particular concern was that the sponsor did not evaluate the contribution of amoxicillin 1 gram b.i.d. to the efficacy of triple therapy. Literature studies suggest that amoxicillin is less likely to contribute antimicrobial activity as compared to clarithromycin. This is evidenced by observations presented in this NDA and in the literature that amoxicillin-PPI dual therapy given at varied doses and frequencies is less effective than clarithromycin-PPI dual therapy. The sponsor reviewed their clinical development program with the FDA and presented across-study comparisons for a two-week clarithromycin/PPI dual therapy (Abbott studies M93-100, and M93-067), a two-week amoxicillin/omeprazole therapy (Astra-Merck studies 035 and 036), and the current 10 day amoxicillin/clarithromycin/omeprazole triple therapy studies. One of the difficulties with across-study comparisons (including this comparison) is that the study protocols may not be similar enough to warrant pooling and/or comparing data from one study to another. In this case, the duration of therapy differed (14 versus 10 days for the dual and triple therapies, respectively), the dosing of clarithromycin and amoxicillin differed (t.i.d. for the dual therapies and b.i.d for the triple therapy), and the dosing of omeprazole differed (40 mg bid for the triple therapy, 20 mg bid for the omeprazole/amoxicillin dual therapy, and 40 mg qd for the omeprazole/clarithromycin dual therapy). With the exception of the last difference (in omeprazole dosing), the difference in dosing frequency and duration of treatment would be more likely to favor the dual therapy over triple therapy making the demonstration of the contribution of amoxicillin (and clarithromycin) more difficult. Otherwise, the study designs for all three types of regimens were similar except that the clarithromycin/omeprazole dual therapy studies did not follow-up patients for *H. pylori* eradication who were found to have an unhealed ulcer at the end of therapy. The sponsor attempted to correct for this difference in the study design by conducting the "per-protocol" eradication analyses in patients who had a healed ulcer at the end of therapy (for the studies M93-100 and M93-067). The eradication rates for these three regimens are presented in Table 64 below.

TABLE 64
***H. pylori* Eradication at 4 to 6 Weeks Post-Treatment**
Per-Protocol and Intent-to-Treat Analyses
Contribution of Amoxicillin and Clarithromycin

Regimen	O 40 qd + C 500 tid for 14 days[1]	O 20 bid + A 1000 tid for 14 days[2]	O 40 mg bid + A 1000 bid + C 500 bid for 10 days[3]
Per-Protocol Combined Analysis	78/114 (68%)	44/89 (49%)	162/193 (84%)
Intent-to-Treat Combined Analysis	84/147 (57%)	47/110 (43%)	181/241 (75%)

1. studies M93-100 and M93-067 combined (these rates were calculated excluding patients that had unhealed ulcer at the end of treatment who were dropped from the study per-protocol).
2. Astra Merck studies 035 and 036 combined
3. Astra Merck studies 126 and 127 and study M96-466 combined

This "across-study comparison" is supportive of the contribution of amoxicillin and clarithromycin to the triple therapy regimen. Given that both clarithromycin and amoxicillin were given for a longer duration and given more frequently in the dual therapy studies as compared with the triple therapy studies, this comparison was biased in favor of dual therapy.

In addition to the above across study comparisons, the sponsor also submitted the results of a European study (M94-183) which compared omeprazole 20 qd + amoxicillin 1 gram b.i.d. + clarithromycin 500 mg b.i.d. for 10 days to omeprazole 40 mg qd + clarithromycin 500 mg t.i.d. for 14 days. The per-protocol and intent-to-treat rates are shown in Table 65.

TABLE 65
***H. pylori* Eradication at 4 to 6 Weeks Post-Treatment**
Per-Protocol and Intent-to-Treat Analyses
O+A+C vs. O+C Study M94-183

	O 20 qd + A 1000 bid + C 500 bid for 10 days	O 40 qd + C 500 tid for 14 days	Pairwise Treatment Group Comparison (using Fisher's Exact Test)
	n/N (%) [95% CI]	n/N (%) [95% CI]	O+A+C vs. O+C P-Value
Per-Protocol	115/127 (91%) [85%, 96%]	68/115 (59%) [50%, 68%]	$p < 0.001$
Intent-to-Treat	120/136 (88%) [83%, 94%]	72/130 (55%) [47%, 64%]	$p < 0.001$

Although the triple therapy regimen was not identical (omeprazole was 20 mg qd) to the proposed U.S. regimen, this direct comparison showing the contribution of amoxicillin favors the dual therapy study arm since clarithromycin was given for longer duration and more frequent doses.

The contribution of omeprazole was demonstrated in all three pivotal studies submitted to this application (studies 126, 127 and M96-446) as seen in Table 66.

TABLE 66
***H. pylori* Eradication at 4 to 6 Weeks Post-Treatment**
Per-Protocol and Intent-to-Treat Analyses
Comparison of O+A+C vs A+C (Studies 126, 127, M96-446)

	O 20 bid + A 1000 bid + C 500 bid for 10 days	A 1000 bid + C 500 bid for 10 days	Pairwise Treatment Group Comparisons (Using logistic regression)
H.pylori Eradicated at 4 to 6 Weeks Post-Treatment	n/N (%) [95% CI]	n/N (%) [95% CI]	O+A+C vs. A+C P-Value
Study 126 PP	49/63 (78%) [68%, 88%]	29/65 (45%) [33%, 57%]	p < 0.001
Study 126 ITT	55/80 (69%) [59%, 79%]	31/84 (37%) [27%, 47%]	p < 0.001
Study 127 PP	51/61 (84%) [74%, 93%]	28/66 (42%) [31%, 54%]	p < 0.001
Study 127 ITT	56/77 (73%) [63%, 83%]	30/83 (36%) [26%, 46%]	p < 0.001
Study M96-446 PP	62/69 (90%) [83%, 97%]	31/93 (33%) [24%, 43%]	p < 0.001
Study M96-446 ITT	70/84 (83%) [75%, 91%]	32/99 (32%) [23%, 42%]	p < 0.001
All three studies combined PP	162/193 (84%) [79%, 89%]	88/224 (39%) [33%, 46%]	p < 0.001
All three studies combined ITT	181/241 (75%) [70%, 81%]	93/266 (35%) [29%, 41%]	p < 0.001

Although the sponsor also submitted the results of a literature-based meta-analysis comparing different dual and triple therapy regimens, a meaningful comparison of eradication rates was not possible since the doses of individual agents and lengths of treatments varied markedly across studies.

EMERGING RESISTANCE

To show an additional contribution of amoxicillin to the combined regimen, the sponsor compared the number of patients with emerging resistance following treatment and compared these results for the O + A + C b.i.d 10 day triple therapy regimens (Astra-Merck 126 and

127 and Abbott study M96-466) to the O + C 14 day regimens (studies M93-067 and M93-100). The MIC breakpoints were as follows:

- susceptible $\leq$ 0.125 mcg/mL
- intermediate > 0.125 mcg/mL and $\leq$ 2 mcg/mL,
- resistant >2 mcg/mL.

For the O + C studies MIC breakpoints using the broth dilution technique were as follows:

- susceptible $\leq$ 0.06 mcg/mL
- intermediate > 0.06 mcg/mL and $\leq$ 2 mcg/mL
- resistant > 2 mcg/mL

Table 67 compares emerging resistance of omeprazole 20 mg b.i.d. + clarithromycin 500 mg b.i.d. + amoxicillin 1 gram b.i.d. x 10 days with clarithromycin 500 mg b.i.d. + amoxicillin 1 gram b.i.d. x 10 days and omeprazole 40 mg qd + clarithromycin 500 mg t.i.d. x 14 days.

Medical Officer's Comment: The emerging resistance rate for patients with susceptible isolates pre-treatment who had H. pylori eradication results post treatment (i.e., failed treatment) was 3 of 10 patients (or 33%) as compared with 25 of 26 (96%) for O + C dual therapy (See Table 67.)

In contrast, a similar calculation for C + A is 10 of 83 failures (12%). These data suggest that amoxicillin "contributes" to reducing emerging resistance when given together with clarithromycin in contrast to omeprazole when given together with clarithromycin.

Among the patients with susceptible isolates pretreatment, there were more patients with no susceptibility result post treatment among those who were not eradicated of *H. pylori* at the follow-up visit for triple therapy (44%, 8/18) as compared with antibiotics alone (18%, 20/111) and omeprazole + clarithromycin therapy (0%, 0/26).

Statistical Reviewer's Comment: The high amount of missing susceptibility data in the triple therapy arm complicates the conclusion about the contribution of amoxicillin to reducing emerging resistance.

TABLE 67
Comparison of Baseline and Post-Treatment *H. pylori* Susceptibility Results
Susceptibility to Clarithromycin Based on Etest® for O+A+C
and Broth Dilution for O+C Number of Patients
All Patients Considered *H. pylori* Infected at Baseline
Comparison of O+A+C and A + C (Studies 126,127,M96-446) and
O+C (Studies M93-067,M93-100)

		Post Treatment *H. pylori* Susceptibility Results to Clarithromycin †						
Baseline *H. pylori* Susc. to Clarithromycin	*H. pylori* Eradicated	*H. pylori* Not Eradicated					No *H.pylori* Eradication Results	Total
		Res.	*Int.*	*Susc.*	*NoResult*	*Total*		
Triple Therapy								
Resistant	4	6	0	1	3	10	1	15
Intermediate	0	0	0	0	0	0	0	0
Susceptible	153	3*	0	7	8	18	19	190
Total	157	9	0	8	11	28	20	205
A 1000 bid + C 500 bid								
Resistant	2	21	0	0	1	22	2	26
Intermediate	0	2	0	0	1	3	0	3
Susceptible	73	10	8	73	20	111	21	205
Total	75	33	8	73	22	136	23	234
O 40 qd + C500 t.i.d.								
Resistant	0	4	0	0	0	4	0	4
Intermediate	0	2	0	0	0	2	0	2
Susceptible	72	25*	‡	‡	‡	26	0	98
Total	72	31	‡	‡	‡	32	0	104

† Post-treatment is defined as 4 to 6 weeks post-treatment for Studies 126, 127, and M96-446, but includes all post-treatment evaluations for Studies M93-067 and M93-100.

‡ The BIAXIN® package insert does not identify the susceptibility status for the one remaining *H. pylori* isolate which was not eradicated.

* The rate of emergent clarithromycin resistance for *H. pylori* isolates was significantly less for the O 20 bid + A 1000 bid + C 500 bid treatment group (3 out of 190 patients with baseline clarithromycin susceptible isolates) than the O 40 qd + C 500 tid treatment group (25 out of 98 patients with isolates susceptible to clarithromycin at baseline), using Fisher's Exact Test ($p<0.001$).

ACTIVE ULCER VERSUS PATIENTS WITH A HISTORY OF ULCER

There has been much controversy regarding the true clinical benefit of patients who have a history of ulcers but do not have a current active duodenal ulcer. The impact of *H. pylori* eradication on ulcer recurrence has not been systematically studied in this population and the acceptance of *H. pylori* eradication as a surrogate for the reduction of ulcer recurrence risk was based on studies that enrolled patients with active ulcers. A recent *H. pylori* approval allowed the inclusion of patients with a history of ulcer disease within the past year to be included in the INDICATIONS AND USAGE section of the label since these patients were included in the pivotal studies.

A recent U.S. H. pylori Consensus Conference (McLean, Virginia 2/1997) recommended treatment of patients with H. pylori-associated active ulcers and patients with active or documented past history of duodenal ulcer, gastric ulcer, and complicated duodenal or gastric ulcer (Gastro 1997;113:S4-S8).

This is in contrast to the NIH Consensus H. pylori Conference Statement in 1994 which stated that "all patients with gastric or duodenal ulcers who are infected with H. pylori should be treated with antimicrobials regardless of whether they are suffering from the initial presentation of the disease or from a recurrence." Without prospective studies which evaluate the clinical impact of H. pylori eradication among patients with H. pylori infection and a history of ulcers, it is difficult to know if this patient group should be treated.

The evaluation of eradication rates between patients with a history of ulcers and active ulcers has been performed in across-study comparisons in two applications submitted to the agency (Astra Merck studies 035 vs. 036 and the current application).
The previous Astra-Merck U.S. application which evaluated omeprazole + amoxicillin in patients with a history of ulcer (study 036) and compared eradication rates to those in study 035 which enrolled patients with active ulcers. The 95% confidence intervals for the difference in eradication rates ("per-protocol" analysis and "ITT analysis) are provided in Table 68.

Table 68. Eradication Rate Comparison for Patients With and Without "Active" Duodenal Ulcer in Studies 035 and 036 Using Amoxicillin 1 gram t.i.d. + Omeprazole 20 mg b.i.d.

Analyses	Active DU	History of DU	
	Study 035 % [95% CI]	Study 036 % [95% CI]	95% Confidence Interval of Difference
"ITT"	N=62 40% [28-53]	N=48 46% [32-60]	[-26.0, 15.0]
"Per-Protocol"	N=52 46% [33-60]	N=37 54% [38-70]	[-31.2, 15.4]

Medical Officer's Comments: Given the wide 95% confidence intervals it is not possible to draw any conclusions about the similarity of the eradication rates in these two studies. Differences in the way H. pylori eradication was assessed may also limit the ability to compare eradication rates across these studies. Eradication was assessed at Week 8 in study 035 and at Week 6 in study 036. However, eradication was assessed at 4 weeks after the end of treatment in both studies. If infection was suppressed in some patients at Week 6 but recurred by Week 8 in study 035, this would tend to lower the "observed" eradication rates in this study as compared with study 036. In addition, study 036 used 2 endoscopic tests to define eradication while study 035 used three endoscopic tests. This difference would again tend to lower the eradication rate for study 035 as compared with study 036 because of the increased chance of "false positive results" when using three tests as compared with two tests. Hence, there are several factors which may complicate the ability to draw conclusions about the similarity of eradication rates between these two regimens.

Despite the limited information regarding the clinical relevance of a past history of ulcers, there is some data (including data presented in this application) which addresses the utility of using the eradication rates generated from varied patient groups (patients with a history of ulcer versus active ulcer patients, respectively) to support a marketing claim for alternative patient groups (patients with active ulcer versus patients with a history of ulcer, respectively).

In the current triple therapy application, the studies which evaluated active ulcer patients were sponsored by a different company than the study which evaluated patients with a history of ulcer disease. Nevertheless, after careful review of the analytic methods and protocol design, this reviewer could not explain the large difference in eradication rates seen among these studies between these two types of patient groups. Table 63 summarizes the eradication rates across studies which evaluated patients with active ulcers versus those with a history of ulcers within the past 5 years. It can be seen that the eradication rates for triple therapy are higher among patients with a history of ulcer disease as compared with patients with active ulcer. In contrast, the opposite is true for the dual therapy arms.

Table 63 Eradication Rates Among Patients with an Active Ulcer as Compared with Patients with a History of Ulcer Within the Past 5 Years (Astra-Merck Studies 126 and 127 are Combined)

	Triple therapy	Dual Therapy
Per-Protocol (Active DU)	80.6% (100/124)	43.5% (57/131)
Per-Protocol (Hx of DU)	90% (62/69)	33% (31/93)
ITT (Active DU)	81% (111/137)	36.5% (61/167)
ITT (Hx of DU)	83% (70/84)	32% (32/99)

Medical Officer Comment: These results do not allow one to conclude that patients with a history of ulcer disease are more or less easy to cure of H. pylori as compared with patients with active ulcer. Hence, it would seem reasonable to extrapolate the eradication results of a study which included patients with a history of ulcer disease to support a claim in patients with an active ulcer.

Medical Officer Comment: The most recent ADHF recommendations did not specify a time point at which H. pylori positive ulcer treatment would not be recommended in patients with duodenal ulcer disease. This point was discussed with the Sponsor in a teleconference call on May 27, 1998. In this meeting, it was pointed out the recently approved lansoprazole triple therapy (lansoprazole + clarithromycin + amoxicillin) and dual therapy (lansoprazole + amoxicillin) was limited to patients with an active ulcer and a history of ulcers within 1 year. Although the current application did have one study which included patients with a history of ulcers up to 5-6 years in the past, there is no data to suggest that these patients will have a reduced incidence of ulcer recurrence following eradication of H. pylori as compared with patients not eradicated of H. pylori. It was agreed with the Sponsor that the labeling for the 10-day triple therapy regimen will be limited to the treatment of patients with active ulcers and patients with a history of ulcers within 1 year.

MAIN CONCLUSIONS

EFFFICACY

The U.S. pivotal studies in this application clearly demonstrate the superiority of a 10 day regimen of omeprazole 20 mg bid + clarithromycin 500mg bid + amoxicillin 1 gram bid over antibiotics alone (amoxicillin 1 gram bid + clarithromycin 500 mg bid). The across-study comparisons and single direct comparison of triple therapy (omeprazole at 20 mg qd + clarithromycin 500 mg b.i.d. + amoxicillin 1 gram b.i.d. for 10 days) to dual therapy (omeprazole 40 mg qd + clarithromycin 500 mg t.i.d. for 2 weeks), strongly suggest that a dual therapy regimen consisting of omeprazole 20 mg b.i.d. + clarithromycin 500 mg b.i.d. when given at 10 days would be less efficacious that the proposed 10 day triple therapy, supporting the contribution of amoxicillin to the efficacy of triple therapy. Previously submitted data using amoxicillin 1 gram t.i.d + omeprazole 20 mg b.i.d. for 2 weeks strongly suggests the contribution of clarithromycin to the proposed triple therapy regimen.

The range in eradication rates for this omeprazole-based 10-day triple therapy was wider (per protocol eradication rates = 78%, 84%, and 90%; ITT eradication rate = 69%, 73%, 83%) than the range reported for the previously-approved 14 day lansoprazole-based triple therapy (per-protocol eradication rate = 92%, and 86%; ITT eradication rate = 83% and 86%) and similar to the rate for the lansoprazole 10 day triple therapy (per-protocol = 84%, ITT rate = 81%). Although the lower-bound 95% confidence interval for the point-estimate of the ITT eradication rate fell below 60% for Astra Merck study 126, the proposed threshold as stated in the DAIDP [Draft] review criteria document, the sponsor did have two studies which had a lower bound 95% confidence limit of 75% and 63%, respectively, using the ITT analysis.

OVERCOMING PRE-TREATMENT RESISTANCE

Please see the FDA MICROBIOLOGY REVIEW for final conclusions regarding overcoming pre-treatment clarithromycin resistance. Of the 15 patients in the triple therapy arm, 4 were eradicated of *H. pylori*. In contrast 2 of 26 patients and 0 of 4 patients were eradicated of *H. pylori* among those who had resistant isolates pre-treatment in the dual antimicrobial arm of the current application and dual therapy (O + C) arm of the Abbott studies, respectively. This suggests that triple therapy may be more effective in *H. pylori* eradication among those who have clarithromycin resistant isolates pre-treatment. Nevertheless, the high rate of failure regardless of which clarithromycin-containing regimen, suggests that *H. pylori* regimens not containing clarithromycin should be considered if clarithromycin resistance pre-treatment is detected.

EMERGING RESISTANCE

Please see the FDA MICROBIOLOGY REVIEW for final conclusions regarding emerging resistance using revised breakpoints. However, the sponsor's emerging resistance data generated from this study was of interest since the antimicrobial alone arms were associated with a very low rate of emerging resistance (12%, 10/83) among those who failed therapy. In contrast, studies 067 and 100 (omeprazole 40 mg qd + clarithromycin 500 mg t.i.d.) and studies (RBC 400 mg b.i.d + clarithromycin 500 mg b.i.d or t.i.d.) had high emerging clarithromycin resistance rates. For the clarithromycin t.i.d. arm, 77% (14/18) developed resistant strains among failures who had susceptible isolates pre-therapy. For the

clarithromycin b.i.d. arm 86% (12/14) developed resistant strains among failures who had susceptible isolates pre-therapy.

When evaluating patients who received triple therapy, only 10 of 18 patients who failed treatment and had susceptible isolates pre-treatment had cultures available post-treatment. Hence, the association between eradication failure and emerging resistance with triple therapy was not clearly documented. Nevertheless, among the 10 patients with susceptible isolates pre-treatment who failed treatment and had cultures available post-treatment, only 3 developed emerging clarithromycin resistance.

The calculation of "intent-to-treat" emerging resistance rates provide another interesting approach to the evaluation of the effect of treatment. Intent-to-treat resistance is defined as the number of patients who develop clarithromycin resistance following treatment over the number of patients who have a susceptible isolate pre-treatment and have eradication results post-treatment. Defined in this was, the "intent-to-treat" emerging resistance rates for triple therapy, dual antimicrobial therapy, and O/C therapy (: studies) were 2% (3/171), 5% (10/184), and 25% (25/98). If patients with an "intermediate" category post treatment are considered resistant, the "intent-to-treat" emerging resistance rate is 10% (18/184) for the antimicrobial alone regimen and does not change for the other arms. Hence, from a "emerging resistance" perspective, it appears that dual antimicrobial therapy is more desirable than omeprazole + clarithromycin.

SAFETY

Although the incidence of diarrhea was high (14%) as compared with other triple therapy regimens given for a longer duration (7%), there were very few patients who dropped out of the study secondary to adverse events. In addition, there were no cases of C-difficile colitis reported in patients treated with triple therapy.

RECOMENDATIONS

It is recommended that the application be approved. However, a number of labeling changes should be made to assist health care providers with prescribing.

LABELING RECOMMENDATIONS

Clinical Studies

The section titled "*Duodenal Ulcer Recurrence*" should be changed to "*H. pylori Eradication in Patients with Duodenal Ulcer Disease*".

Under the section titled "Triple Therapy" (PRILOSEC/clarithromycin/amoxicillin), the table describing the eradication rates for triple therapy and antibiotic-only dual therapy should be changed to present both per-protocol and ITT eradication rates. The following table should replace the existing table which shows the per-protocol *H. pylori* eradication rates:

Per-Protocol and Intent-to-Treat *H. pylori* Eradication Rates [95% Confidence Interval]

	PRILOSEC + clarithromycin + amoxicillin		Clarithromycin + amoxicillin	
	Per-Protocol †	Intent-to-Treat‡	Per-Protocol†	Intent-to-Treat‡
Study 126	*77% [64, 86] (n = 64)	*69% [57, 79] (n = 80)	43% [31, 56] (n = 67)	37% [27, 48] (n = 84)
Study 127	*78% [67, 88] (n = 65)	*73% [61, 82] (n = 77)	41% [29, 54] (n = 68)	36% [26, 47] (n = 83)
Study M96-446	*90% [80, 96] (n = 69)	*83% [74, 91] (n = 84)	33% [24, 44] (n = 93)	32% [23, 42] (n = 99)

† Patients were included in the analysis if they had confirmed duodenal ulcer disease (active ulcer, studies 126 and 127; history of ulcer within 5 years, study M96-446) and *H. pylori* infection at baseline defined as at least two of three positive endoscopic tests from CLOtest®, histology and/or culture. Patients were included in the analysis if they completed the study. Additionally, if patients dropped out of the study due to an adverse event related to the study drug, they were included in the analysis as failures of therapy. The impact of eradication on ulcer recurrence has not been assessed in patients with a past history of ulcer.
‡ Patients were included in the analysis if they had documented *H. pylori* infection at baseline and had confirmed duodensl ulcer disease. All dropouts were included as failures of therapy.
* ($p < 0.05$) versus clarithromycin plus amoxicillin.

For recommendations regarding resistance information in the clinical trial section, please see the MICROBIOLOGY REVIEW/comments.

The entire section under "Dual Therapy" should be consistent with the Clarithromycin label. This section should read as follows:

"Four randomized, double-blind, multi-center studies (067, 100, 812b, and 058) evaluated clarithromycin 500 mg t.i.d. plus omeprazole 40 mg q.d. for 14 days, followed by omeprazole 20 mg q.d. (067, 100, 058) or by omeprazole 40 mg q.d. (812b) for an additional 14 days in patients with active duodenal ulcer associated with *H. pylori*. Studies 067 and 100 were conducted in the U.S. and Canada and enrolled 242 and 256 patients, respectively. *H. pylori* infection and duodenal ulcer were confirmed in 219 patients in Study 067 and 228 patients in Study 100. These studies compared the combination regimen to omeprazole and clarithromycin monotherapies. Studies 812b and 058 were conducted in Europe and enrolled 154 and 215 patients, respectively. *H. pylori* infection and duodenal ulcer were confirmed in 148 patients in Study 812b and 208 patients in Study 058. These studies compared the combination regimen to omeprazole monotherapy. The results for the efficacy analyses for these studies are described below. *H. pylori* Eradication was defined as no positive test (culture or histology) at 4 weeks following the end of treatment, and two negative tests were

required to be considered eradicated of *H. pylori*. In the per-protocol analysis, the following patients were excluded: dropouts, patients with missing *H. pylori* tests post-treatment, and patients that were not assessed for *H. pylori* eradication because they were found to have an ulcer at the end of treatment."

The table describing the *H. pylori* eradication rates for dual therapies should be revised to be consistent with the clarithromycin package insert. The following table should replace the existing table which describes *H. pylori* eradication rates.

H. pylori Eradication Rates (Per-Protocol Analysis) at 4 to 6 weeks
% of Patients Cured [95% Confidence Interval]

	PRILOSEC + Clarithromycin	PRIOLOSEC	Clarithromycin
U.S. Studies			
Study M93-067	74 [60, 85]†‡ (n = 53)	0 [0, 7] (n = 54)	31 [18, 47] (n = 42)
Study M93-100	64 [51, 76] †‡ (n = 61)	0 [0, 6] (n = 59)	39 [24, 55] (n = 44)
Non-U.S. Studies			
Study M92-812b	83 [71, 92] ‡ (n = 60)	1 [0, 7] (n = 74)	NA
Study 058	74 [64, 83] ‡ (n = 86)	1 [0, 6] (n = 90)	NA

† Statistically significantly higher than clarithromycin monotherapy ($p<0.05$)
‡ Statistically significantly higher than omeprazole monotherapy ($p<0.05$)

The statement describing ulcer healing should not be revised. The statement and table describing the relationship between *H. pylori* eradication and ulcer recurrence with dual therapy should not be revised.

INDICATIONS AND USAGE
The proposed changes to this section are acceptable. However, treatment should not be indicated for patients who have not had an ulcer for > 1 year prior to presentation. The second paragraph of the section titled "*Duodenal Ulcer*" should be changed to "PRILOSEC Delayed-Release Capsules, in combination with clarithromycin and amoxicillin, are indicated for treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or up to 1 year history) to eradicate *H. pylori*.

In addition, this section should be made consistent with the Biaxin package insert with regards to the possibility of emerging resistance for dual therapy as compared with triple therapy.

Hence, the following statement should be deleted:

APPEARS THIS WAY
ON ORIGINAL

/S/ 6/24/98

Robert Hopkins M.D., M.P.H. & T.M.
Medical Team Leader, DSPIDP

/S/ 6/29/98

Nancy Silliman Ph.D.
Statistical Reviewer, DB IV

Concurrence
HFD-590/DivDir/Mark Goldberger /S/ 7/2/98
HFD-725/Acting Stat TL/Aloka Chakravarty /S/ 6/29/98

cc:
Orig. NDA 20-916
HFD-590/MO/Robert Hopkins
HFD-590/CSO/Robin Anderson
HFD-725/Biometrics/Nancy Silliman
HFD-590/Biopharm/Houda Mahaymi
HFD-590/Biopharm Acting TL/Funmilayo Ajayi
HFD-725/Biostat TL/Aloka Chakravarty
HFD-725/Biostat DivDir/Mohammad Huque
HFD-725/Biostat/Sandra Shores
HFD-590/Micro/Linda Utrup
HFD-590/Micro TL/Sheryl Lard
HFD-590/DepDivDir/Renata Albrecht
HFD-590/DivDir/Mark Goldberger

APPEARS THIS WAY
ON ORIGINAL

Approval Recommendation: Approval

APPEARS THIS WAY
ON ORIGINAL

JUN 2 9 1998

Medical Safety Update Review for New Drug Application #20-916

General Information:

Applicant Name:	Astra Merck, Inc.
Applicant's Address:	725 Chesterbrook Blvd., Wayne, PA 19087
Applicant's Telephone:	(610) 695-1008

Submission/Review Dates:

Date of Submission:	January 30, 1998
Date of Receipt:	February 2, 1998
Date Received by Reviewer:	February 3, 1998
Date Review Completed:	June 29, 1998

Drug Identification:

Generic Name	Omeprazole (with amoxicillin and clarithromycin)
Pharmacologic Category:	substituted benzimidazole
Proposed Trade Name:	Prilosec®
Chemical Name:	$C_{17}H_{19}N_3O_3S$
Weight:	345.42
Dosage Form:	Delayed-Release Capsules
Route of Administration:	Oral

Volumes Reviewed: 3

Resume:

The Safety Update Report contains clinical safety information from five completed clinical trials available to Astra Merck after the original NDA was submitted. The report also contains an update on serious adverse events reported in clinical trials and obtained through post-marketing surveillance between March 31, 1997 and September 30, 1997. The five studies included in the report are shown below.

- Astra-Hassle: The effect of omeprazole on the efficacy of clarithromycin plus either amoxicillin or metronidazole for the treatment of *H. pylori* associated duodenal ulcer disease (SH-OMH-0005). The total enrolled was 539.
- Astra-Hassle: Eradication of *H. pylori* and ulcer healing in DU-patients with omeprazole in combination with clarithromycin plus either amoxicillin or metronidazole (SH-OMH-0006). The total enrolled was 149.
- Astra Hassle: Eradication of *H. pylori* and ulcer healing in gastric ulcer patients with omeprazole in combination with clarithromycin plus either amoxicillin or metronidazole (Study No. SH-OMH-007). The total enrolled was 160.
- Astra Merck: A multicenter, open label, randomized study to compare the tolerability of ten day omeprazole triple therapy to fourteen day standard triple therapy in

subjects receiving treatment for *H. pylori* eradication (Protocol 115) (not included in this submission). The total enrolled was 160.

- Astra Hassle: An interaction study between omeprazole, amoxicillin, and clarithromycin (SH-OMH-0016). The total number enrolled was 16.

The study design, treatments, gender/race characteristics, age range, and duration of treatment for each study are summarized in the Attachment (Table 1, Table of Clinical Studies).

The sponsor also summarized adverse events temporally related to treatment with omeprazole, amoxicillin, and clarithromycin used in combination for *H. pylori*-related diseases. There were 5 patients with the following non-fatal serious adverse events though "unlikely" to be related to the study medication: kidney stone, myocardial infarction, hernia, intervertebral disc, malignant hepatic neoplasm, renal carcinoma.

Eight patients with non-fatal serious adverse events were obtained through post-marketing surveillance. The following AEs with relationship to study drugs reported as "unknown" were: Belching, black stools, increased frequency of stools, exacerbation of hair loss, fatigue, "feeling groggy", hypoglycemia, cerebral vascular accident, sore throat, hot flushes, and lump in throat. The relationship to study drugs was "unknown" for all cases. AEs with "possible" relationship to study drug were: thrombocytopenia, Stevens Johnson Syndrome, Deafness, and Urticaria.

One patient had a fatal serious AE with an "unknown" relationship to the study regimen. This patient had a history of type 1 diabetes mellitus and gastric ulcer and was hospitalized with asthenia, anorexia, abdominal pain, fever and chills. The patient had a history of omeprazole use at the time of hospitalization and had also been taking amoxicillin and clarithromycin for *H. pylori* eradication. The patient had leukocytosis, occult blood in stools, a heterogeneous mass in the epigastrium, and various hypodense hepatic lesions. Peripancreatic and retroperitoneal adenopathies were found. Biopsy of a deep gastric ulcer lesion showed inflammatory material with gram positive cocci. Purulent material from a hepatic biopsy cultured streptococcus viridans and the same organism was cultured from the blood. The patient died after 2 days of imipenem and metronidazole in a state of septic shock. No autopsy was performed.

Medical Officer Comment: The triple therapy regimen used in the patient was unlikely to contribute the death of this patient.

The number of patients with adverse events by system organ class and by adverse event term are listed in the Attachment for each study.

For the largest study (SH-0MH-0005), the number of adverse events are presented below along side the AE's reported in the ISS of the original NDA for studies 126, 127, and M96-446.

The Percent of Patients Who Had a Specified Clinical Adverse Event by Body System Category for OCA Triple Therapy in Pivotal Studies Submitted to NDA 20-916 and Study SH-OMH-005

Clinical Adverse Event by Body System	O 20 bid + A 1000 bid + C 500 bid ISS Data from Studies 126, 127 and M96-446 Percent n=274	O 20 bid + A 1000 bid +C 500 bid Study SH-OMH-005 Percent n=132
Gastrointestinal System		
Diarrhea	13.9	28.8
Nausea	4.4	3.0
Abdominal Pain	4.0	0.8
Vomiting	2.9	0
Flatulence	1.8	0
Special Senses		
Taste Perversion	9.9	21.3
Central and Peripheral Nervous System		
Headache	6.6	3.0
Respiratory System		
Sinusitis	2.9	N/A
Respiratory Infection	2.6	N/A
Pharyngitis	2.2	N/A
Body as a Whole		
Back Pain	2.6	N/A
Psychiatric		
Insomnia	1.8	0

In study SH-OMH-005, there were 3 patients who stopped study medications due to adverse events who received the OCA treatment.- Adverse events leading to withdrawal included nausea, metallic taste and abdominal pain, and diarrhea. None were considered

serious. The results of this study and the other studies included in this submission are presented in the Attachment (Table 2).

Medical Officer's Comment: The incidence of diarrhea was higher in this study as compared with the data submitted in the ISS for the original NDA. This study was conducted in Europe. Hence, the incidence of AEs from this study may not accurately reflect AE incidence in the U.S. No other clinically significant differences were seen in this study as compared with studies presented in the ISS of the original NDA.

Main Medical Officer's Conclusions
Although the incidence of diarrhea was higher in study SH-OMH-0005 as compared to studies 126, 127, and M96-446, there were no clinically significant differences in incidence or occurrence of other adverse events in the clinical studies submitted in the current submission as compared with the original NDA. The adverse event data from the original NDA more accurately reflects incidence in the U.S. population.

Medical Officer's Recommendations
The Updated Safety Report does not support any labeling changes for the combination therapy Omeprazole + clarithromycin + amoxicillin.

/S/

Robert Hopkins M.D., M.P.H. & T.M.
Medical Team Leader, DSPIDP

Concurrence
HFD-590/DivDir/Mark Goldberger /S/6

APPEARS THIS WAY
ON ORIGINAL

cc:
Orig. NDA 20-916
HFD-590/MO/Robert Hopkins
HFD-590/Biostat/Nancy Silliman
HFD-590/Biostat/Aloka Chakravarty
HFD-590/Micro/Linda Utrup
HFD-590/Micro TL/Sheryl Lard
HFD-590/DepDivDir/Renata Albrecht
HFD-590/DivDir/Mark Goldberger

Approval Recommendation: Approval

TABLE 1
Table of Clinical Studies

Ref No.	Study No./ Location	Study Status	Study Design	Treatment/ Doses	Total Enrolled	% Gender Race	Age Range	Duration of Treatment
[Ref(s). 1]	SH-OMH-0005/ 46 centers in Europe	Completed	STUDY DESIGN: Double-blind, randomized, international, multicenter trial, four parallel groups in patients with history of duodenal ulcer and *H.pylori* infection. STUDY DURATION: 9 weeks OBJECTIVE: To investigate the influence of omeprazole in the eradication of *H.pylori* in patients with duodenal ulcer disease	TREATMENT GROUPS: 1. O 20 mg bid + C 500 mg bid + A 1000 mg bid 2. C 500 mg bid + A 1000 mg bid 3. O 20 mg bid + C 250 mg bid + M 400 mg bid 4. C 250 mg bid + M 400 mg bid	539	Male 66% Female 34% Cauc 98% Black 1% Asian 1%		All Groups =7 days

O = omeprazole; A = amoxicillin; C = clarithromycin; M = metronidazole

APPEARS THIS WAY
ON ORIGINAL

TABLE 1
Table of Clinical Studies (Cont.)

Ref No.	Study No./ Location	Study Status	Study Design	Treatment/ Doses	Total Enrolled	% Gender Race	Age Range	Duration of Treatment
[Ref(s). 2]	SH-OMH-0006/ 15 centers in Canada	Completed	STUDY DESIGN: Double-blind, randomized, multicenter trial, three parallel groups in patients with endoscopically verified duodenal ulcer and *H.pylori* infection. STUDY DURATION: 4 weeks treatment with follow-up at 3 and 6 months OBJECTIVE: To compare eradication rates of *H.pylori* in duodenal ulcer patients between omeprazole alone and a combination therapy with omeprazole, clarithromycin and either amoxicillin or metronidazole. To compare the treatment groups regarding duodenal ulcer relapse during a 6 month period after healing of the ulcer.	TREATMENT GROUPS: 1. O 20 mg bid + C 250 mg bid + M 400 mg bid 2. O 20 mg bid + C 500 mg bid + A 1000 mg bid 3. O 20 mg daily	149	Male 73% Female 27% Cauc 96% Black 1% Asian 2% Other 1%		All Groups =7 days Follow-up treatment for all groups: O 20 mg daily (21 days)

O = omeprazole; A = amoxicillin; C = clarithromycin; M = metronidazole

APPEARS THIS WAY
ON ORIGINAL

TABLE 1 (Cont.)
Table of Clinical Studies

Ref No.	Study No./ Location	Study Status	Study Design	Treatment/ Doses	Total Enrolled	% Gender Race	Age Range	Duration of Treatment
[Ref(s). 3]	SH-OMH-0007/ 18 centers in Germany, Hungary and Poland	Completed	STUDY DESIGN: Double-blind, randomized, international, multicenter trial, three parallel groups in patients with verified gastric ulcer and *H.pylori* infection. STUDY DURATION: 4-12 weeks treatment with follow-up at 3 and 6 months OBJECTIVE: To compare eradication rates of *H.pylori* in gastric ulcer patients between omeprazole alone, and a combination with omeprazole, clarithromycin plus either amoxicillin or metronidazole. To compare gastric ulcer recurrence, during 6 months after healing of the ulcer.	TREATMENT GROUPS: 1. O 20 mg daily 2. O 20 mg bid + C 250 mg bid + M 400 mg bid 3. O 20 mg bid + C 500 mg bid + A 1000 mg bid	160	Male 61% Female 39% Cauc 100%		All Groups =7 days Follow-up treatment for all groups: O 20 mg daily (14 days) Unhealed patients continued to receive omeprazole

O = omeprazole; A = amoxicillin; C = clarithromycin; M = metronidazole

TABLE 1 (Cont.)
Table of Clinical Studies

Ref No.	Study No./ Location	Study Status	Study Design	Treatment/ Doses	Total Enrolled	% Gender Race	Age Range	Duration of Treatment
[Ref(s). 4]	AMI 115/ 18 centers in US	Completed	STUDY DESIGN: Randomized, multicenter, open-label, parallel group study in patients with a history of peptic ulcer disease and current *H.pylori* infection. STUDY DURATION: 6 weeks OBJECTIVE: To assess the gastrointestinal tolerability of a ten day triple therapy regimen of omeprazole, clarithromycin and amoxicillin compared to fourteen day standard triple therapy with bismuth subsalicylate, tetracycline and metronidazole in subjects with *H.pylori*-infection and a history of peptic ulcer disease. To assess the overall tolerability of a ten day triple therapy regimen of omeprazole, clarithromycin and amoxicillin compared to fourteen day standard triple therapy with bismuth subsalicylate, tetracycline and metronidazole in subjects with *H.pylori*-infection and a history of peptic ulcer disease	TREATMENT GROUPS: 1. O 20 mg bid + A 1000 mg bid + C 500 mg bid 2. B 2 tabs qid + T 500 mg qid + M 250 mg qid	160	Male 58.1% Female 41.9% Cauc 81.9% Black 15.6% Asian 1.9% Other 0.6%		Group 1 = 10 days Group 2 = 14 days

O = omeprazole; A = amoxicillin; C = clarithromycin; B = Bismuth; T = tetracycline; M = metronidazole

TABLE 1 (Cont.)
Table of Clinical Studies

Ref No.	Study No./ Location	Study Status	Study Design	Treatment/ Doses	Total Enrolled	% Gender Race	Age Range	Duration of Treatment
[Ref(s). 5]	SH-OMH-0016	Completed	STUDY DESIGN: Open label, randomized, four-way crossover study STUDY DURATION: 12 weeks OBJECTIVE: To investigate potential pharmacokinetic drug-drug interactions between omeprazole, amoxicillin and clarithromycin after repeated oral administration in healthy subjects	TREATMENT GROUPS: 1. O 20 mg bid 2. A 1000 mg bid 3. C 500 mg bid 4. O 20 mg bid + A 1000 mg bid + C 500 mg bid	16	Males 62.5% Females 37.5% Race: N/A		All Treatments =7 days (2 week wash-out period between treatments)

O = omeprazole; A = amoxicillin; C = clarithromycin
N/A = not available

APPEARS THIS WAY
ON ORIGINAL

ADVERSE EVENTS

Table 2. Number of patients (%) with adverse events ordered by system organ class. Adverse events are listed as included terms. A single patient may experience more than one AE even under the same system organ class.

Study drug Number of patients Number of patients with adverse event:	OCM (N=133) 60 (45.1)	CM (N=133) 65 (48.9)	OCA (N=132) 69 (52.3)	CA (N=137) 67 (48.9)
SKIN AND APPENDAGES DISORDERS				
Total	2 (1.5)	4 (3.0)	3 (2.3)	5 (3.6)
Eczema	1 (0.8)	0	0	0
Erythema localized	0	0	0	1 (0.7)
Itching	1 (0.8)	1 (0.8)	1 (0.8)	0
Perianal itching	0	0	1 (0.8)	0
Pruritus	0	2 (1.5)	0	1 (0.7)
Pruritus ani	0	1 (0.8)	1 (0.8)	0
Pruritus genital	0	0	0	1 (0.7)
Seborrhoea	0	0	0	1 (0.7)
Vaginal itching	0	0	0	1 (0.7)
MUSCULO-SKELETAL SYSTEM DISORDERS				
Total	1 (0.8)	0	0	0
Cramps legs	1 (0.8)	0	0	0
CENTR & PERIPH NERV SYST DISORDERS				
Total	2 (1.5)	5 (3.8)	6 (4.5)	5 (3.6)
Dizziness	1 (0.8)	2 (1.5)	0	1 (0.7)
Headache	1 (0.8)	2 (1.5)	4 (3.0)	4 (2.9)
Migraine	0	1 (0.8)	0	0
Paraesthesia arms	0	0	1 (0.8)	0
Restless legs	0	0	0	1 (0.7)
Tremor	0	0	1 (0.8)	0
VISION DISORDERS				
Total	1 (0.8)	0	0	0
Iridocyclitis	1 (0.8)	0	0	0
SPECIAL SENSES OTHER, DISORDERS				
Total	9 (6.8)	4 (3.0)	14 (10.6)	17 (12.4)
Taste bad	3 (2.3)	1 (0.8)	1 (0.8)	4 (2.9)
Taste bitter	2 (1.5)	0	3 (2.3)	3 (2.2)
Taste metallic	3 (2.3)	1 (0.8)	8 (6.1)	6 (4.4)
Taste perversion	1 (0.8)	2 (1.5)	2 (1.5)	4 (2.9)
PSYCHIATRIC DISORDERS				
Total	1 (0.8)	1 (0.8)	0	0
Impotence	0	1 (0.8)	0	0
Insomnia	1 (0.8)	0	0	0
GASTRO-INTESTINAL SYSTEM DISORDERS				
Total	32 (24.1)	38 (28.6)	56 (42.4)	50 (36.5)
Abdominal discomfort	0	0	0	1 (0.7)
Abdominal pain	0	1 (0.8)	1 (0.8)	1 (0.7)
Abdominal pain lower	0	0	1 (0.8)	0
Acid regurgitation	0	1 (0.8)	0	0
Belching	0	1 (0.8)	0	0
Bloating	1 (0.8)	1 (0.8)	2 (1.5)	0
Borborygmus	1 (0.8)	0	0	1 (0.7)
Diarrhoea	13 (9.8)	14 (10.5)	38 (28.8)	37 (27.0)

ADVERSE EVENTS

Dyspepsia	1 (0.8)	1 (0.8)	0	0
Epigastric pain	0	2 (1.5)	0	1 (0.7)
Flatulence	2 (1.5)	3 (2.3)	0	3 (2.2)
Flatus	0	1 (0.8)	0	0
Gastric pain	0	0	1 (0.8)	0
Gastroenteritis	1 (0.8)	0	0	0
Glossitis	1 (0.8)	0	0	0
Heartburn	0	0	0	1 (0.7)
Meteorism	2 (1.5)	2 (1.5)	0	2 (1.5)
Mouth dry	2 (1.5)	2 (1.5)	1 (0.8)	0
Mouth irritation	1 (0.8)	1 (0.8)	0	0
Mouth sore	2 (1.5)	0	3 (2.3)	1 (0.7)
Nausea	1 (0.8)	4 (3.0)	4 (3.0)	2 (1.5)
Perianal redness	0	0	1 (0.8)	0
Stomach pain	0	1 (0.8)	1 (0.8)	0
Stomatitis	0	0	0	1 (0.7)
Stool black	0	0	2 (1.5)	0
Stool tarry	0	0	1 (0.8)	0
Stools loose	7 (5.3)	6 (4.5)	6 (4.5)	6 (4.4)
Tongue coated	0	1 (0.8)	0	0
Tongue disorder	0	0	1 (0.8)	0
Tongue white	0	0	1 (0.8)	0
Vomiting	0	0	0	2 (1.5)
LIVER AND BILIARY SYSTEM DISORDERS				
Total	20 (15.0)	13 (9.8)	3 (2.3)	6 (4.4)
ALAT increased	17 (12.8)	12 (9.0)	2 (1.5)	4 (2.9)
ASAT increased	12 (9.0)	8 (6.0)	1 (0.8)	3 (2.2)
Cholecystitis	1 (0.8)	0	0	0
Hepatic enzymes increased nos	1 (0.8)	1 (0.8)	1 (0.8)	0
Liver function tests abnormal	0	0	0	1 (0.7)
METABOLIC AND NUTRITIONAL DISORDERS				
Total	2 (1.5)	1 (0.8)	1 (0.8)	2 (1.5)
Creatinine serum increased	0	0	1 (0.8)	0
Glycosuria	1 (0.8)	1 (0.8)	0	0
Phosphatase alkaline increased	0	0	0	2 (1.5)
Thirst	1 (0.8)	0	0	0
CARDIOVASCULAR DISORDERS, GENERAL				
Total	0	0	0	2 (1.5)
Cardiac failure	0	0	0	1 (0.7)
Orthostatic reaction	0	0	0	1 (0.7)
HEART RATE AND RHYTHM DISORDERS				
Total	1 (0.8)	0	0	1 (0.7)
Arrhythmia	1 (0.8)	0	0	0
Atrial fibrillation paroxysmal	0	0	0	1 (0.7)
VASCULAR (EXTRACARDIAC) DISORDERS				
Total	0	0	0	1 (0.7)
Flushing	0	0	0	1 (0.7)
RESPIRATORY SYSTEM DISORDERS				
Total	2 (1.5)	4 (3.0)	3 (2.3)	2 (1.5)

ADVERSE EVENTS

Asthma	0	1 (0.8)	0	0
Coughing	0	1 (0.8)	0	0
Dyspnoea	1 (0.8)	0	0	0
Pharyngitis	0	0	1 (0.8)	1 (0.7)
Pneumonia	0	0	0	1 (0.7)
Throat sore	1 (0.8)	2 (1.5)	2 (1.5)	0
WHITE CELL AND RES DISORDERS				
Total	0	0	1 (0.8)	0
Lymph nodes enlarged	0	0	1 (0.8)	0
URINARY SYSTEM DISORDERS				
Total	3 (2.3)	2 (1.5)	1 (0.8)	3 (2.2)
Dysuria	0	0	0	1 (0.7)
Erythrocytes urine, strip	2 (1.5)	1 (0.8)	1 (0.8)	1 (0.7)
Haematuria	0	0	0	1 (0.7)
Proteinuria	1 (0.8)	1 (0.8)	0	0
REPRODUCTIVE DISORDERS, FEMALE				
Total	0	0	1 (0.8)	2 (1.5)
Vaginal discharge	0	0	0	1 (0.7)
Vaginitis	0	0	0	1 (0.7)
Vulvovaginitis	0	0	1 (0.8)	0
BODY AS A WHOLE - GENERAL DISORDERS				
Total	5 (3.8)	3 (2.3)	1 (0.8)	4 (2.9)
Abdominal distension	0	1 (0.8)	0	0
Ache legs	1 (0.8)	0	0	0
Allergic reaction	0	0	0	1 (0.7)
Asthenia	1 (0.8)	0	0	0
Concussion brain	0	1 (0.8)	0	0
Fatigue	0	1 (0.8)	0	0
Laboratory test abnormal nos	1 (0.8)	0	0	1 (0.7)
Oedema	0	0	0	1 (0.7)
Pain scar	0	0	1 (0.8)	0
Tiredness	3 (2.3)	0	0	1 (0.7)
RESISTANCE MECHANISM DISORDERS				
Total	2 (1.5)	2 (1.5)	2 (1.5)	1 (0.7)
Candidiasis oral	1 (0.8)	0	1 (0.8)	0
Influenza	1 (0.8)	2 (1.5)	1 (0.8)	0
Moniliasis genital	0	0	0	1 (0.7)

APPEARS THIS WAY
ON ORIGINAL

ADVERSE EVENTS

Table 2. Number (%) of patients with adverse events ordered by system organ class.

DRUG:	OCA	OCM	Omeprazole	Open Omeprazole	Follow-up
No. of patients:	n=50	n=49	n=50	n=147	n=143
SKIN AND APPENDAGES DISORDERS					
Total	1 (2.0)	0	2 (4.0)	9 (6.1)	0
Hives	0	0	0	1 (0.7)	0
Itching	1 (2.0)	0	0	1 (0.7)	0
Itching generalized	0	0	1 (2.0)	1 (0.7)	0
Itching rash	0	0	0	1 0.7)	0
Perianal itching	0	0	0	1 (0.7)	0
Rash	0	0	1 (2.0)	1 (0.7)	0
Rash face	0	0	0	1 (0.7)	0
Vaginal itching	0	0	0	2 (1.4)	0
MUSCULO-SKELETAL SYSTEM DISORDERS					
Total	0	0	1 (2.0)	4 (2.7)	0
Bursitis	0	0	0	1 (0.7)	0
Hernia hiatal	0	0	0	2 (1.4)	0
Joint swelling,knees	0	0	0	0	0
Knee pain	0	0	0	1 (0.7)	0
Tendinitis aggravated	0	0	1 (2.0)	1 (0.7)	0
CENTR & PERIPH NERV SYST DISORDERS					
Total	7 (14.0)	7 (14.3)	6 (12.0)	14 (9.5)	0
Dizziness	0	0	2 (4.0)	4 (2.7)	0
Dysphonia	1 (2.0)	0	0	1 (0.7)	0
Headache	5 (10.0)	6 (12.2)	4 (8.0)	9 (6.1)	0
Hyperactivity	1 (2.0)	0	0	1 (0.7)	0
Light-headed feeling	0	1 (2.0)	0	0	0
Numbness lips,tongue	1 (2.0)	0	0	1 (0.7)	0
Tremor	1 (2.0)	0	0	1 (0.7)	0
VISION DISORDERS					
Total	0	0	0	1 (0.7)	0
Eye symptoms nos	0	0	0	1 (0.7)	0
HEARING AND VESTIBULAR DISORDERS					
Total	0	0	1 (2.0)	1 (0.7)	0
Ear infection nos	0	0	1 (2.0)	1 (0.7)	0
SPECIAL SENSES OTHER, DISORDERS					
Total	10 (20.0)	5 (10.2)	1 (2.0)	12 (8.2)	0
Taste alteration	0	1 (2.0)	0	1 (0.7)	0
Taste bitter	1 (2.0)	0	1 (2.0)	1 (0.7)	0
Taste metallic	7 (14.0)	3 (6.1)	0	7 (4.8)	0
Taste perversion	2 (4.0)	1 (2.0)	0	3 (2.0)	0

ADVERSE EVENTS

PSYCHIATRIC DISORDERS					
Total	5 (10.0)	2 (4.1)	2 (4.0)	8 (5.4)	0
Anxiety	1 (2.0)	0	0	1 (0.7)	0
Appetite decreased	0	0	0	1 (0.7)	0
Appetite lost	1 (2.0)	0	0	1 (0.7)	0
Confusion	0	1 (2.0)	0	1 (0.7)	0
Drowsiness	0	0	1 (2.0)	0	0
Insomnia	1 (2.0)	0	0	1 (0.7)	0
Libido decreased	1 (2.0)	0	0	1 (0.7)	0
Sleep disorder	1 (2.0)	0	0	1 (0.7)	0
Sleep disturbed	0	1 (2.0)	0	0	0
Trembling inside	0	0	1 (2.0)	1 (0.7)	0
GASTRO-INTESTINAL SYSTEM DISORDERS					
Total	29 (58.0)	17 (34.7)	13 (26.0)	54 (36.7)	0
Abdominal pain	1 (2.0)	1 (2.0)	1 (2.0)	3 (2.0)	0
Anal discomfort	0	0	0	1 (0.7)	0
Bloating	0	1 (2.0)	0	1 (0.7)	0
Blood in stool-	0	0	0	1 (0.7)	0
Constipation	3 (6.0)	0	2 (4.0)	2 (1.4)	0
Cramp abdominal	1 (2.0)	0	0	0	0
Diarrhoea	13 (26.0)	7 (14.3)	4 (8.0)	8 (5.4)	0
Dyspepsia	1 (2.0)	1 (2.0)	1 (2.0)	8 (5.4)	0
Epigastric pain	1 (2.0)	0	1 (2.0)	4 (2.7)	0
Flatulence	3 (6.0)	1 (2.0)	0	3 (2.0)	0
Haemorrhage rectum	0	0	0	2 (1.4)	0
Haemorrhoids	0	0	0	2 (1.4)	0
Heartburn	1 (2.0)	2 (4.1)	0	3 (2.0)	0
Mouth dry	2 (4.0)	1 (2.0)	0	2 (1.4)	0
Nausea	3 (6.0)	4 (8.2)	2 (4.0)	12 (8.2)	0
Oesophageal pain	0	0	1 (2.0)	1 (0.7)	0
Oesophagitis	0	0	0	1 (0.7)	0
Oral dryness	0	0	0	1 (0.7)	0
Rectal disorder	1 (2.0)	0	0	1 (0.7)	0
Rectal pain	1 (2.0)	0	0	1 (0.7)	0
Regurgitation	0	0	0	1 (0.7)	0
Stomach cramps	1 (2.0)	0	0	1 (0.7)	0
Stools frequent	0	0	0	1 (0.7)	0
Stools loose	5 (10.0)	4 (8.2)	2 (4.0)	9 (6.1)	0
Tongue black	0	0	0	1 (0.7)	0
Tongue blisters	0	0	0	1 (0.7)	0
Tongue inflammation	2 (4.0)	0	0	3 (2.0)	0
Tongue sore	0	0	0	2 (1.4)	0
Vomiting	0	1 (2.0)	2 (4.0)	4 (2.7)	0
LIVER AND BILIARY SYSTEM DISORDERS					
Total	0	2 (4.1)	1 (2.0)	7 (4.8)	0
S-GPT increased	0	2 (4.1)	1 (2.0)	6 (4.1)	0
S-GOT increased	0	1 (2.0)	1 (2.0)	3 (2.0)	0
METABOLIC AND NUTRITIONAL DISORDERS					
Total	0	1 (2.0)	0	1 (0.7)	0
Glycosuria	0	1 (2.0)	0	1 (0.7)	0

ADVERSE EVENTS

RESPIRATORY SYSTEM DISORDERS					
Total	3 (6.0)	3 (6.1)	1 (2.0)	15 (10.2)	0
Asthma aggravated	0	0	0	1 (0.7)	0
Common cold	3 (6.0)	1 (2.0)	0	9 (6.1)	0
Coughing	0	0	0	2 (1.4)	0
Coughing,dry	0	1 (2.0)	0	0	0
Nose congestion	0	0	0	2 (1.4)	0
Rhinitis	0	0	0	1 (0.7)	0
Sinuses congested	0	0	1 (2.0)	1 (0.7)	0
Throat sore	0	1 (2.0)	0	4 (2.7)	0
RED BLOOD CELL DISORDERS					
Total	0	0	0	1 (0.7)	0
Haemoglobin decreased	0	0	0	1 (0.7)	0
WHITE CELL AND RES DISORDERS					
Total	0	0	0	1 (0.7)	0
Wbc decreased	0	0	0	1 (0.7)	0
URINARY SYSTEM DISORDERS					
Total	3 (6.0)	1 (2.0)	2 (4.0)	8 (5.4)	1 (0.7)
Erythrocytes urine, strip	2 (4.0)	0	0	2 (1.4)	0
Haematuria	1 (2.0)	1 (2.0)	0	2 (1.4)	0
Kidney stone	0	0	0	1 (0.7)	0
Proteinuria	1 (2.0)	0	0	3 (2.0)	1 (0.7)
Urinary bladder infection	0	0	1 (2.0)	1 (0.7)	0
Urinary tract infection	0	0	1 (2.0)	1 (0.7)	0
BODY AS A WHOLE - GENERAL DISORDERS					
Total	4 (8.0)	3 (6.1)	2 (4.0)	15 (10.2)	0
Accident and/or injury	0	0	0	2 (1.4)	0
Back pain (lumbago)	1 (2.0)	0	0	2 (1.4)	0
Chest pain	1 (2.0)	0	0	1 (0.7)	0
Chills	0	0	1 (2.0)	1 (0.7)	0
Fatigue	1 (2.0)	1 (2.0)	0	2 (1.4)	0
Flu-like disorder	0	0	0	1 (0.7)	0
Injury hand	0	0	0	1 (0.7)	0
Malaise	0	0	0	1 (0.7)	0
Pain leg	1 (2.0)	0	0	0	0
Pain neck	1 (2.0)	0	0	2 (1.4)	0
Tiredness	0	2 (4.1)	0	1 (0.7)	0
Weakness generalized	0	0	1 (2.0)	1 (0.7)	0
RESISTANCE MECHANISM DISORDERS					
Total	1 (2.0)	0	1 (2.0)	4 (2.7)	0
Candidiasis oral	0	0	0	1 (0.7)	0
Herpes simplex	1 (2.0)	0	1 (2.0)	2 (1.4)	0
Influenza	0	0	0	1 (0.7)	0

AEs are listed as included term. A single patient may experience more than one AE even under the same system organ class. The ASTRA Adverse Event Dictionary (AED) used is based on and structured like the WHO terminology.

CLINICAL STUDY REPORT
REPORT NO: SH-OMH-0007

APPENDIX 1

ADVERSE EVENTS

Table 2. Number of patients (%) with adverse events ordered by system organ class. Adverse events are listed as included terms. A single patient may experience more than one AE even under the same system organ class.

Study drug	OCM	OCA	O	O open treatment 20 mg o.m.
Number of patients:	(N=53)	(N=52)	(N=52)	(N=156)
Number of patients with adverse event:	8 (15.1)	5 (9.6)	5 (9.6)	25 (16.0)
SKIN AND APPENDAGES DISORDERS				
Total	0	0	0	2 (1.3)
Dermatitis allergic	0	0	0	1 (0.6)
Exanthema	0	0	0	1 (0.6)
CENTR & PERIPH NERV SYST DISORDERS				
Total	0	1 (1.9)	0	2 (1.3)
Gait disturbance	0	0	0	1 (0.6)
Paraesthesia tongue	0	1 (1.9)	0	1 (0.6)
Tremor	0	0	0	1 (0.6)
SPECIAL SENSES OTHER, DISORDERS				
Total	4 (7.5)	3 (5.8)	1 (1.9)	5 (3.2)
Taste acid	2 (3.8)	0	0	0
Taste metallic	2 (3.8)	3 (5.8)	1 (1.9)	5 (3.2)
PSYCHIATRIC DISORDERS				
Total	1 (1.9)	0	1 (1.9)	3 (1.9)
Anorexia	1 (1.9)	0	1 (1.9)	2 (1.3)
Anxiety	0	0	0	1 (0.6)
GASTRO-INTESTINAL SYSTEM DISORDERS				
Total	2 (3.8)	3 (5.8)	2 (3.8)	5 (3.2)
Constipation	0	0	1 (1.9)	1 (0.6)
Diarrhoea	1 (1.9)	1 (1.9)	0	1 (0.6)
Oral dryness	0	0	1 (1.9)	1 (0.6)
Stomatitis	1 (1.9)	0	0	0
Stools loose	0	2 (3.8)	0	2 (1.3)
LIVER AND BILIARY SYSTEM DISORDERS				
Total	0	0	1 (1.9)	3 (1.9)
increased	0	0	0	2 (1.3)
ASAT increased	0	0	1 (1.9)	3 (1.9)
METABOLIC AND NUTRITIONAL DISORDERS				
Total	2 (3.8)	0	1 (1.9)	7 (4.5)
Phosphatase alkaline increased	1 (1.9)	0	0	4 (2.6)
Weight decrease	1 (1.9)	0	1 (1.9)	3 (1.9)

APPEARS THIS WAY ON ORIGINAL

Cont. Table 2. Number of patients (%) with adverse events ordered by system organ class. Adverse events are listed as included terms. A single patient may experience more than one AE even under the same system organ class.

Study drug	OCM	OCA	O	O open treatment 20 mg o.m.
RESPIRATORY SYSTEM DISORDERS				
Total	0	0	1 (1.9)	1 (0.6)
Bronchitis	0	0	1 (1.9)	1 (0.6)
WHITE CELL AND RES DISORDERS				
Total	1 (1.9)	0	0	4 (2.6)
Leukocytosis	1 (1.9)	0	0	2 (1.3)
Leukopenia	0	0	0	1 (0.6)
Multiple myeloma	0	0	0	1 (0.6)
PLATELET,BLEEDING & CLOTTING DISORDERS				
Total	0	0	0	2 (1.3)
Platelets decreased	0	0	0	2 (1.3)
URINARY SYSTEM DISORDERS				
Total	1 (1.9)	0	1 (1.9)	2 (1.3)
Polyuria	0	0	1 (1.9)	1 (0.6)
Urinary tract infection	1 (1.9)	0	0	1 (0.6)
Urine wbc increased	0	0	0	1 (0.6)
REPRODUCTIVE DISORDERS, FEMALE				
Total	0	0	1 (1.9)	1 (0.6)
Vaginal discomfort	0	0	1 (1.9)	1 (0.6)
NEOPLASMS				
Total	1 (1.9)	0	2 (3.8)	3 (1.9)
Gastric carcinoma	0	0	0	1 (0.6)
Pancreatic neoplasm malignant	0	0	1 (1.9)	1 (0.6)
Renal carcinoma	1 (1.9)	0	0	1 (0.6)
Uterine carcinoma	0	0	1 (1.9)	0
BODY AS A WHOLE - GENERAL DISORDERS				
Total	0	0	0	1 (0.6)
Injury leg	0	0	0	1 (0.6)
RESISTANCE MECHANISM DISORDERS				
Total	0	0	0	1 (0.6)
Influenza	0	0	0	1 (0.6)

Table 2. Number of patients with Adverse Events ordered by system organ class.

Drug: No of subjects:	Omeprazole 20 mg bid (n=16)	Amoxicillin 1000 mg bid (n=16)	Clarithromycin 500 mg bid (n=16)	OAC (n=16)	TOTAL (n=16)
No. of subjects with Adverse Event:	6 (37.5)	9 (56.3)	11 (68.8)	16 (100.0)	16 (100.0)
SKIN AND APPENDAGES DISORDERS	**0**	**1**	**0**	**1**	**1**
Itching rash	0	1	0	1	1
MUSCULO-SKELETAL SYSTEM DISORDERS	**0**	**1**	**0**	**0**	**1**
Muscle pain	0	1	0	0	1
CENTR & PERIPH NERV SYST DISORDERS	**0**	**0**	**2**	**8**	**8**
Dizziness	0	0	0	1	1
Headache	0	0	2	7	7
SPECIAL SENSES OTHER, DISORDERS	**0**	**0**	**4**	**7**	**7**
Taste bad	0	0	4	7	7
PSYCHIATRIC DISORDERS	**0**	**0**	**0**	**1**	**1**
Anorexia	0	0	0	1	1
GASTRO-INTESTINAL SYSTEM DISCORD.	**6**	**6**	**6**	**11**	**13**
Constipation	0	0	1	0	1
Diarrhoea	0	0	1	3	3
Flatulence	4	1	1	2	6
Griping abdominal	1	1	0	1	3
Nausea	1	1	0	2	4
Stomach pain	1	1	2	1	2
Stools loose	0	5	3	9	11
LIVER AND BILIARY SYSTEM DISORDERS	**0**	**1**	**0**	**0**	**1**
ALAT increased	0	1	0	0	1
ASAT increased	0	1	0	0	1
METABOLIC AND NUTRITIONAL DISORD.	**0**	**1**	**1**	**0**	**2**
Blood sugar decreased	0	0	1	0	1
LDH increased	0	1	0	0	1

cont.

Table 2. cont.

Drug:	Omeprazole 20 mg bid	Amoxicillin 1000 mg bid	Clarithromycin 500 mg bid	OAC	TOTAL
No of subjects:	(n=16)	(n=16)	(n=16)	(n=16)	(n=16)
RESPIRATORY SYSTEM DISORDERS	**1**	**4**	**1**	**2**	**6**
Common cold	1	4	1	2	6
WHITE CELL AND RES DISORDERS	**0**	**0**	**1**	**0**	**1**
Eosinophilia	0	0	1	0	1
WBC increased	0	0	1	0	1
URINARY SYSTEM DISORDERS	**0**	**1**	**0**	**0**	**1**
Blood in urine	0	1	0	0	1
REPRODUCTIVE DISORDERS, FEMALE	**0**	**1**	**1**	**0**	**1**
Menses painful	0	1	1	0	1
BODY AS A WHOLE - GENERAL DISORD.	**1**	**1**	**0**	**0**	**2**
Back pain	0	1	0	0	1
Fever	1	0	0	0	1

OAC = omeprazole 20 mg bid + amoxicil lin 1000 mg bid + clarithromycin 500 mg bid

APPEARS THIS WAY
ON ORIGINAL

Table 3. Number of subjects with new onset Adverse Events during the wash-out periods, i.e., adverse events that occurred during a wash-out period, without having been present during the preceding treatment period.

	Wash-out after Omeprazole (n=16)	Wash-out after Amoxicillin (n=16)	Wash-out after Clarithromycin (n=16)	Wash-out after OAC (n=16)
No. of subjects with new onset adverse events:	3	2	2	2
CENTR & PERIPH NERV SYST DISORDERS	**1**	**0**	**0**	**0**
Headache	1	0	0	0
GASTRO-INTESTINAL SYSTEM DISORDERS	**0**	**1**	**0**	**0**
Griping abdominal	0	1	0	0
RESPIRATORY SYSTEM DISORDERS	**1**	**1**	**2**	**2**
Common cold	1	1	2	2
REPRODUCTIVE DISORDERS, FEMALE	**1**	**0**	**0**	**0**
Menses painful	1	0	0	0

OAC = omeprazole 20 mg bid + amoxicillin 1000 mg bid + clarithromycin 500 mg bid

APPEARS THIS WAY
ON ORIGINAL